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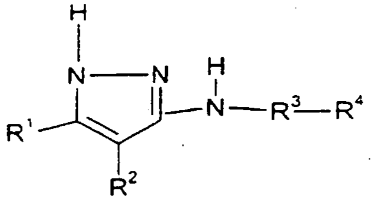
(54) **Title:** PYRAZOLE DERIVATIVES AND THEIR USE AS PROTEIN KINASE INHIBITORS



(1)

(57) **Abstract:** The invention provides compounds of formula (1) wherein R^1, R^2, R^3, and R^4 are as defined, and their pharmaceutically acceptable salts. Compounds of formula (1) are indicated to have activity inhibiting cdk2, and GSK-3. Pharmaceutical compositions and methods comprising compounds of formula (1) for treating and preventing diseases and conditions comprising abnormal cell growth, such as cancer, and neurodegenerative diseases and conditions and those affected by dopamine neurotransmission. Also described are pharmaceutical compositions and methods comprising compounds of formula (1) for treating male fertility and sperm motility; diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and obesity; myogenesis and frailty, for example age-related decline in physical performance; acute sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency.

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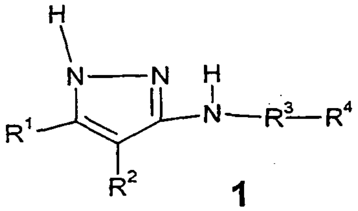
Acta 1114:147-162) (1992)). Due to a remarkably high degree of conservation across the phylogenetic spectrum, a fundamental role of GSK-3 in cellular processes is suggested.

GSK-3 has been implicated in numerous different disease states and conditions. For example, Chen, et al, *Diabetes* 43: 1234-1241 (1994) have suggested that an increase in GSK-3 activity can be important in Type 2 diabetes. Increased GSK-3 expression in diabetic muscle is also though to contribute to the impaired glycogen synthase activity and skeletal muscle insulin resistance present in Type 2 diabetes (Nikoulina, et al., *Diabetes* 49: 263-271 (2000)). Also, a higher activity of a type 1 protein phosphatase measured in immotile sperm was attributed to higher GSK-3 activity and was indicated as responsible for holding the sperm motility in check (Vijayaraghavan, et al. *Biology of Reproduction* 54: 709-718 (1996)). Vijayaraghavan et al. indicate that such results suggest a biochemical basis for the development and regulation of sperm motility and a possible physiological role for a protein phosphatase 1/inhibitor 2/GSK-3 system. GSK-3 activity has also been associated with Alzheimer's disease and mood disorders such as bipolar disorder (WO 97/41854). Among other conditions, GSK-3 has furthermore been implicated in hair loss, schizophrenia, and neurodegeneration, including both chronic neurodegenerative diseases (such as Alzheimer's, *supra*) and neurotrauma, for example stroke, traumatic brain injury, and spinal cord trauma.

Summary of the Invention

This invention provides compounds of the formula



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wherein R^1 is a straight chain or branched (C_1-C_8)alkyl, a straight chain or branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, or (5-11 membered) heterobicycloalkyl; and wherein R^1 is optionally substituted with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, and R^7;

R^2 is H, F, $-CH_3$, -CN, or $-C(=O)OR^7$;

R^3 is $-C(=O)NR^9-$, $-C(=O)O-$, $-C(=O)(CR^{10}R^{11})_n-$, or $-(CR^{10}R^{11})_n-$;

$-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}C(=O)NR^{17}R^{18}$, $-NR^{16}S(=O)_2R^{17}$, $-NR^{16}S(=O)_2NR^{17}R^{18}$ $-OR^{16}$, $-OC(=O)R^{16}$, $-OC(=O)OR^{16}$, $-OC(=O)NR^{16}R^{17}$, $-OC(=O)SR^{16}$, $-SR^{16}$, $-S(=O)R^{16}$, $-S(=O)_2R^{16}$, $-S(=O)_2NR^{16}R^{17}$, $-C(=O)R^{16}$, $-C(=O)OR^{16}$, $-C(=O)NR^{16}R^{17}$, and R^{16}

each R^{16}, R^{17}, and R^{18} is independently selected from H, straight chain or branched $(C_1$-$C_8)$alkyl, straight chain or branched $(C_2$-$C_8)$alkenyl, straight chain or branched $(C_2$-C_8 alkynyl), $(C_3$-$C_8)$cycloalkyl, $(C_4$-$C_8)$cycloalkenyl, (3-8 membered) heterocycloalkyl, $(C_5$-$C_{11})$bicycloalkyl, $(C_7$-$C_{11})$bicycloalkenyl, (5-11 membered) heterobicycloalkyl, $(C_6$-$C_{14})$aryl, and (5-14 membered) heteroaryl;

n is 0, 1, 2, or 3;

wherein R^{10} and R^{11} in $-C(=O)(CR^{10}R^{11})_n-$ and $-(CR^{10}R^{11})_n-$ are for each iteration of n defined independently as recited above;

and pharmaceutically acceptable salts thereof.

Amino-substituted pyrazoles can exist as mixtures of tautomeric isomers in equilibrium with one another. The present invention includes all such tautomers of compounds of formula **1**, and references herein to compounds of formula **1**, unless otherwise indicated, encompass also the tautomers of compounds of formula **1**.

Compounds of formula **1** of the invention are inhibitors of serine/threonine kinases, especially cyclin-dependent kinases such as cdk5 and cdk2, and are useful for the treatment of neurodegenerative disorders and other CNS disorders, and of abnormal cell growth, including cancer. The compounds of formula **1** are particularly useful in inhibiting cdk5. The compounds of formula **1** are also useful as inhibitors of GSK-3.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and *t*-butyl.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl.

The term "cycloalkyl", as used herein, unless otherwise indicated, includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. "Bicycloalkyl" groups are non-aromatic saturated carbocyclic groups consisting of two rings, wherein said rings share one or two carbon atoms. For purposes of the present invention, and unless otherwise indicated, bicycloalkyl groups include spiro groups and fused

pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.

The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). The terms referring to the groups also encompass all possible tautomers.

In one embodiment, this invention provides compounds of formula **1**, wherein R^3 is $-C(=O)NR^9-$ or $-C(=O)(CR^{10}R^{11})_n-$. In another embodiment, R^{10} and R^{11} of $-C(=O)(CR^{10}R^{11})_n-$ are at each iteration of n both hydrogen. In another embodiment, R^9 of $-C(=O)NR^9-$ is hydrogen. In another embodiment, R^3 is $-C(=O)NR^9-$ or $-C(=O)(CR^{10}R^{11})_n-$ and R^2 is hydrogen. In another embodiment, R^3 is $-(CR^{10}R^{11})_n-$, and n is zero. In a preferred embodiment R^3 is $-(CR^{10}R^{11})_n-$, n is zero, and R^4 is (C_6-C_{14})aryl or (5-14 membered) heteroaryl, each optionally substituted as recited above.

In another embodiment of the invention, a compound of formula **1** is provided wherein R^1 is optionally substituted (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl. Preferred embodiments are wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or norbornyl, each optionally substituted as recited above (i.e. optionally with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, and R^7). In a more preferred embodiment, R^1 is (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or norbornyl, and is optionally substituted with from one to three substituents independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, and R^7. More preferably, R^1 is (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or norbornyl, and R^1 is substituted with $-NR^7C(=O)R^8$, (C_6-C_{14})aryl, (3-8 membered) heterocycloalkyl, or (5-14 membered) heteroaryl, and wherein said aryl, heterocycloalkyl, and heteroaryl are each optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{10}R^{11}$, $-NR^{10}C(=O)R^{11}$, $-NR^{10}C(=O)OR^{11}$, $-NR^{10}C(=O)NR^{11}R^{12}$, $-NR^{10}S(=O)_2R^{11}$, $-NR^{10}S(=O)_2NR^{11}R^{12}$, $-OR^{10}$, $-OC(=O)R^{10}$, $-OC(=O)OR^{10}$, (5-cyclobutyl-2H-pyrazol-3-yl)-(3-methoxy-phenyl)-amine;

(5-cyclobutyl-2H-pyrazol-3-yl)-(4-nitro-phenyl)-amine;

(4-chloro-benzyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

(3-bromo-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

(5-cyclobutyl-2H-pyrazol-3-yl)-quinolin-2-yl-amine;

[5-(1,4-dioxa-spiro[4.4]non-7-yl)-1H-pyrazol-3-yl]-(3-trifluoromethyl-phenyl)-amine;

(6-chloro-pyridin-2-yl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentanone;

(5-cyclobutyl-2H-pyrazol-3-yl)-(6-methoxy-4-methyl-quinolin-2-yl)-amine;

(5-cyclobutyl-2H-pyrazol-3-yl)-(3-trifluoromethoxy-phenyl)-amine;

(2-chloro-4-nitro-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

3-*trans*-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentanol;

(3,5-bis-trifluoromethyl-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

[5-(3-*cis*-benzylamino-cyclopentyl)-1H-pyrazol-3-yl]-(3-trifluoromethyl-phenyl)-amine;

{5-[3-*cis*-(4-methoxy-benzylamino)-cyclopentyl]-1H-pyrazol-3-yl}-(3-trifluoromethyl-phenyl)-amine;

4-(5-cyclobutyl-2H-pyrazol-3-ylamino)-benzonitrile;

(5-cyclobutyl-2H-pyrazol-3-yl)-(3-fluoro-phenyl)-amine;

(5-cyclobutyl-2H-pyrazol-3-yl)-(3,5-dichloro-phenyl)-amine;

(2-bromo-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

N-{*cis*-3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-acetamide;

pyridin-2-yl-{3-*trans*-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amine;

(5-cyclobutyl-1H-pyrazol-3-yl)-(4-methoxy-phenyl)-amine;

pyridine-2-carboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide;

3-trifluoromethyl-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-benzamide;

cyclobutanecarboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide;

2,2-dimethyl-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-propionamide;

4-fluoro-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-benzamide;

2,2,2-trifluoro-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-acetamide;

pyrazine-2-carboxylic acid {*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide;

4-methoxy-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide;

N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-3-nitro-benzamide;

N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-3-trifluoromethyl-benzamide;

N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-isobutyramide;

2-phenyl-cyclopropanecarboxylic acid {*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide;

N-{5-[*cis*-3-(benzooxazol-2-yloxy)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

4-dimethylamino-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide;

3,5-dimethoxy-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide;

2-naphthalen-1-yl-N-[5-(*cis*-3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(3-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[*cis*-3-(4-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

2-naphthalen-1-yl-N-[5-(*cis*-3-*p*-tolyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(4-chloro-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

2-(4-methoxy-phenyl)-N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-phenyl-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-pyridin-3-yl-acetamide;

N-{5-[*cis*-3-(4-methoxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

2-quinolin-6-yl-N-[5-(*cis*-3-*p*-tolyl-cyclobutyl)-1H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(4-fluoro-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[3-(6-methyl-pyridin-2-yloxy)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[3-(6-chloro-benzothiazol-2-yloxy)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[3-(6-methoxy-benzothiazol-2-yloxy)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide; and

pharmaceutically acceptable salts of the foregoing compounds.

Other examples of preferred compounds of formula **1** are:

N-{5-[*cis*-3-(4-Hydroxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(3-Hydroxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

2-Naphthalen-1-yl-N-[5-(*cis*-3-pyridin-3-yl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-[5-(*cis*-3-Naphthalen-2-yl-cyclobutyl)-2H-pyrazol-3-yl]-2-pyridin-3-yl-acetamide;

N-(5-Indan-2-yl-1H-pyrazol-3-yl)-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-Pyridin-2-yl-cyclobutyl)-2H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-Pyridin-2-yl-cyclobutyl)-2H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

2-(4-Methoxy-phenyl)-N-[5-(*cis*-3-pyridin-4-yl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[3-(*cis*-2-Dimethylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[3-(2-Dimethylamino-ethoxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Hydroxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[2-(2-Dimethylamino-ethoxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-[5-(*cis*-3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(2-Fluoro-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[4-(Azetidin-3-yloxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[2-(Azetidin-3-yloxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[*cis*-3-(2-methylsulfanyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(2-Amino-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[*cis*-3-(3-propylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(3-Cyclopentylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[3-(Benzylamino-methyl)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[3-(3-methylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(3-Cyclopropylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[*cis*-3-(3-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(3-Diethylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(3-Azetidin-1-ylmethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

and pharmaceutically acceptable salts of the foregoing compounds.

Other specific examples of compounds of the invention of formula **1** are:

N-[5-(*cis*-3-pyridin-2-yl-cyclobutyl)-1H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-pyridin-3-yl-cyclobutyl)-1H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-pyridin-4-yl-cyclobutyl)-1H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-pyrazin-2-yl-cyclobutyl)-1H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-pyrimidin-4-yl-cyclobutyl)-1H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(3-methoxy-pyridin-2-yl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(4-methoxy-pyridin-3-yl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(3-methoxy-pyridin-4-yl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(2-methoxy-pyridin-3-yl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(5-methoxy-pyrimidin-4-yl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(1-ethyl-1H-imidazol-2-yl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-(3-hydroxy-phenyl)-acetamide;

N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-phenyl-acetamide;

2-(4-chloro-phenyl)-N-(5-cyclopentyl-2H-pyrazol-3-yl)-acetamide;

N-(5-cyclopentyl-1H-pyrazol-3-yl)-2-naphthalen-2-yl-acetamide;

N-(5-cyclobutyl-2H-pyrazol-3-yl)-2-(2,4-dichloro-phenyl)-acetamide;

N-(5-cyclobutyl-2H-pyrazol-3-yl)-2-quinolin-6-yl-acetamide;

2-(3-amino-phenyl)-N-(5-cyclobutyl-2H-pyrazol-3-yl)-acetamide;

1-(5-cyclobutyl-1H-pyrazol-3-yl)-3-naphthalen-1-yl-urea;

N-(5-cyclohexyl-1H-pyrazol-3-yl)-2-naphthalen-2-yl-acetamide;

N-(5-cyclohexyl-1H-pyrazol-3-yl)-2-phenyl-acetamide;

2-(4-chloro-phenyl)-N-(5-cyclohexyl-1H-pyrazol-3-yl)-acetamide;

N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-(4-phenoxy-phenyl)-acetamide;

N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-(4-dimethylamino-phenyl)-acetamide;

N-(5-cyclopentyl-2H-pyrazol-3-yl)-2-(2,3,4-trimethoxy-phenyl)-acetamide;

N-(5-cyclopentyl-2H-pyrazol-3-yl)-2-(4-isopropyl-phenyl)-acetamide;

N-(5-cyclopentyl-2H-pyrazol-3-yl)-2-pyrrolo[2,3-b]pyridin-1-yl-acetamide;

N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-m-tolyl-acetamide;

N-(5-cyclopentyl-2H-pyrazol-3-yl)-2-p-tolyl-acetamide;

N-(5-cyclobutyl-1H-pyrazol-3-yl)-2-(3-trifluoromethoxy-phenyl)-acetamide;

N-[5-(3-benzyloxy-propyl)-1H-pyrazol-3-yl]-2-naphthalen-2-yl-acetamide;

4-[5-(2-naphthalen-2-yl-acetylamino)-1H-pyrazol-3-yl]-piperidine-1-carboxylic acid benzyl ester;

2-naphthalen-2-yl-N-(5-piperidin-4-yl-2H-pyrazol-3-yl)-acetamide;

N-[5-(1-acetyl-piperidin-4-yl)-2H-pyrazol-3-yl]-2-naphthalen-2-yl-acetamide;

N-[5-(1-benzoyl-piperidin-4-yl)-2H-pyrazol-3-yl]-2-naphthalen-2-yl-acetamide;

4-[5-(2-naphthalen-1-yl-acetylamino)-1H-pyrazol-3-yl]-piperidine-1-carboxylic acid benzyl ester;

N-[5-(1-cyclobutanecarbonyl-piperidin-4-yl)-2H-pyrazol-3-yl]-2-naphthalen-2-yl-acetamide;

N-{3-[5-(2-naphthalen-2-yl-acetylamino)-4H-pyrazol-3-yl]-propyl}-benzamide;

N-{3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-propyl}-benzamide;

N-{5-[1-(3-methyl-butyl)-piperidin-4-yl]-1H-pyrazol-3-yl}-2-naphthalen-2-yl-acetamide;

N-[3-(5-phenylacetylamino-2H-pyrazol-3-yl)-propyl]-benzamide;

N-{3-[5-(2-m-tolyl-acetylamino)-2H-pyrazol-3-yl]-propyl}-benzamide;

N-(3-{5-[2-(3-chloro-phenyl)-acetylamino]-2H-pyrazol-3-yl}-propyl)-benzamide;

6-methyl-pyridine-2-carboxylic acid (3-{5-[2-(3-methoxy-phenyl)-acetylamino]-2H-pyrazol-3-yl}-cyclobutyl)-amide;

6-methyl-pyridine-2-carboxylic acid (3-{5-[2-(4-methoxy-phenyl)-acetylamino]-2H-pyrazol-3-yl}-cyclobutyl)-amide;

6-methyl-pyridine-2-carboxylic acid (3-{5-[2-(4-chloro-phenyl)-acetylamino]-2H-pyrazol-3-yl}-cyclobutyl)-amide; and

pharmaceutically acceptable salts of said compounds.

Salts of compounds of formula **1** can be obtained by forming salts with any acidic or basic group present on a compound of formula **1**. Examples of pharmaceutically acceptable salts of the compounds of formula **1** are the salts of hydrochloric acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, maleic acid, di-p-toluoyl tartaric acid, acetic acid, sulfuric acid, hydroiodic acid, mandelic acid, sodium, potassium, magnesium, calcium, and lithium.

The compounds of formula **1** may have optical centers and therefore may occur in different enantiomeric and other stereoisomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula **1**, as well as racemic and other mixtures thereof.

The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formula **1**, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula **1** of this invention can of the bladder, breast, colon, kidney, liver, lung, for example small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumor of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; a tumor of mesenchymal origin, for example fibrosarcoma or rhabdomyosarcoma; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In another embodiment, the disease or condition comprising abnormal cell growth is benign. *Such diseases and conditions include benign* prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, fungal infection, and endotoxic shock.

This invention also provides a pharmaceutical composition for treating a neurodegenerative disease or condition in a mammal, including a human, comprising a compound of formula **1** in an amount effective in treating said disease or condition, and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition for treating a neurodegenerative disease or condition in a mammal, including a human, comprising a compound of formula **1** in an amount effective in inhibiting cdk5 activity, and a pharmaceutically acceptable carrier.

This invention also provides a method for treating a neurodegnerative disease or *condition in a mammal, including a human, comprising administering to the mammal a* compound of formula **1** in an amount effective in inhibiting cdk5 activity.

This invention also provides a method for treating a neurodegenerative disease or condition in a mammal, including a human, comprising administering to the mammal a compound of formula **1** in an amount effective in treating said disease or condition.

In one embodiment of the invention, the neurodegenerative disease or condition which is treated is selected from Huntington's disease, stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, epilepsy, amyotrophic lateral sclerosis, pain, viral induced dementia for example AIDS induced dementia, neurodegeneration associated with bacterial infection, migraine, hypoglycemia, urinary incontinece, brain ischemia, multiple sclerosis, Alzheimer's disease, senile dementia of the Alzheimer's type, mild cognitive impairment, agea bipolar disorder, for example bipolar I disorder, bipolar II disorder, cyclothymic disorder; anxiety; attention deficit and hyperactivity disorder; and attention deficit disorder.

This invention also provides a pharmaceutical composition for treating a disease or condition the treatment of which can be effected or facilitated by decreasing cdk5 activity in a mammal, including a human, which composition comprises a compound of formula **1** in an amount effective in inhibiting cdk5 activity and a pharmaceutically acceptable carrier.

This invention also provides a method for treating a disease or condition the treatment of which can be effected or facilitated by decreasing cdk5 activity in a mammal, including a human, which method comprises administering to the mammal a compound of formula **1** in an amount effective in inhibiting cdk5 activity.

We have also found that the compounds of formula **1** have activity in inhibiting GSK-3. The compounds of formula **1** therefore can be expected to be useful in treating diseases and conditions the treatment of which can be effected or facilitated by inhibition of GSK-3. Diseases and conditions the treatment of which can be effected or facilitated by inhibiting GSK-3 include neurodegenerative diseases and conditions. Neurodegenerative diseases and conditions are discussed above and include, but are not limited to, for example Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, cerebral ischemia, AIDS-related dementia, neurodegeneration associated with bacterial infection, multiinfarct dementia, traumatic brain injury, and spinal cord trauma. Therefore, compounds of formula **1** are effective in treating neurodegenerative diseases and conditions based on both cdk5 activity and GSK-3 activity.

Other diseases and conditions the treatment of which can be effected or facilitated by inhibiting GSK-3 include psychotic disorders and conditions, for example schizophrenia, schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type. The treatment of such diseases and conditions can also be effected or facilitated by altering dopamine mediated neurotransmission. Therefore, compounds of formula **1** are effective in treating such disorders and conditions based on both cdk5 activity and GSK-3 activity.

Other disorders and conditions the treatment of which can be effected or facilitated by inhibiting GSK-3 include mood disorders and mood episodes, for example a major depressive episode, a manic or mixed mood episode, a hypomanic mood episode, a depressive episode with atypical features or with melancholic features or catatonic features, a mood episode with postpartum onset; post-stroke depression, major depressive disorder, dysthymic disorder, in physical performance; acute sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency; which method comprises administering to said mammal an amount of a compound of formula **1** effective in treating said disease or condition.

The present invention also provides a method for treating in a mammal, including a human, a disease or condition selected from male fertility and sperm motility; diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and obesity; myogenesis and frailty, for example age-related decline in physical performance; acute sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency; which method comprises administering to said mammal an amount of a compound of formula **1** effective in inhibiting GSK-3.

The present invention further provides a method for inhibiting GSK-3 in a mammal, including a human, which method comprises administering to said mammal an amount of a compound of formula **1** effective in inhibiting GSK-3.

The present invention further provides a pharmaceutical composition for treating in a mammal, including a human, a disorder selected from Alzheimer's disease, mild cognitive impairment, and age-related cognitive decline comprising a compound of formula **1** and a COX-II inhibitor together in an amount effective in treating said disorder, and a pharmaceutically acceptable carrier.

This invention also provides a method for treating in a mammal, including a human, a disorder selected from Alzheimer's disease, mild cognitive impariment, and age-related cognitive decline which method comprises administering to said mammal a compound of formula **1** and a COX-II inhibitor, wherein the combined amounts of the compound of formula **1** and the COX-II inhibitor are effective in treating said disorder. The compound of formula **1** and the COX-II inhibitor can be administered to the mammal at the same time and/or separately. Moreover, the compound of formula **1** and the COX-II inhibitor can be administered in a single composition or in separate compositions.

Moreover, a compound of formula **1** of the invention, or a pharmaceutically acceptable salt of a compound of formula **1**, can be administered or formulated into a pharmaceutical composition with one or more anti-depressants or anxiolytic compounds for treatment or prevention of depression and/or anxiety.

Accordingly, this invention also provides a pharmaceutical composition for treating depression or anxiety in a mammal, including a human, comprising a compound of formula **1**

This invention further provides a method for treating schizophrenia in a mammal, including a human, which method comprises administering to said mammal a compound of formula **1** and an antipsychotic selected from ziprasidone, olanzapine, risperidone, L-745870, sonepiprazole, RP 62203, NGD 941, balaperidone, flesinoxan, and gepirone, wherein the combined amounts of the compound of formula **1** and the antipsychotic are effective in treating schizophrenia. The compound of formula **1** and the antipsychotic can be administered to the mammal at the same time and/or at different times. Moreover, they may be administered together in a single pharmaceutical composition or in separate pharmaceutical compositions.

This invention also provides a pharmaceutical composition for treating a disorder selected from Alzheimer's disease, mild cognitive impairment, and age-related cognitive decline in a mammal, including a human, comprising a compound of formula **1** and an acetylcholinesterase inhibitor together in an amount effective in treating said disorder, and a pharmaceutically acceptable carrier.

This invention further provides a method for treating in a mammal, including a human, a disorder selected from Alzheimer's disease, mild cognitive impairment, and age-related cognitive decline, which method comprises administering to said mammal a compound of formula **1** and an acetylcholinesterase inhibitor, wherein the combined amounts of the compound of formula **1** and the acetylcholinesterase inhibitor are effective in treating said disorder. The compound of formula **1** and the acetylcholinesterase inhibitor can be administered to the mammal at the same time and/or at different times. Moreover, they may be administered together in a single pharmaceutical composition or in separate pharmaceutical compositions.

This invention also provides a pharmaceutical composition for treating a disease or condition selected from stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, epilepsy, pain, Alzheimer's disease, and senile dementia comprising a compound of formula **1** and TPA (tissue plasminogen activator, for example ACTIVASE) together in an amount effective in treating said disorder, and a pharmaceutically acceptable carrier.

This invention further provides a method for treating in a mammal, including a human, a disease or condition selected from stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, epilepsy, pain, Alzheimer's disease, and senile dementia, which method comprises administering to said mammal a compound of formula **1** and TPA, wherein the combined amounts of the compound of formula **1** and the TPA are effective in treating said disease or condition. The compound of formula **1** and the TPA can be administered to the mammal at the same time and/or at different times. Moreover, they may be administered together in a single pharmaceutical composition or in separate pharmaceutical compositions.

This invention also provides a pharmaceutical composition for treating a disease or condition selected from stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, time and/or at different times. Moreover, they may be administered together in a single pharmaceutical composition or in separate pharmaceutical compositions.

This invention also provides a pharmaceutical composition for treating a disease or condition selected from stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, epilepsy, pain, Alzheimer's disease, and senile dementia in a mammal, including a human, comprising a compound of formula **1** and a potassium channel modulator together in an amount effective in treating said disorder, and a pharmaceutically acceptable carrier.

This invention further provides a method for treating in a mammal, including a human, a disease or condition selected from stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, epilepsy, pain, Alzheimer's disease, and senile dementia, which method comprises administering to said mammal a compound of formula **1** and a potassium channel modulator, wherein the combined amounts of the compound of formula **1** and the potassium channel modulator are effective in treating said disease or condition. The compound of formula **1** and the potassium channel modulator can be administered to the mammal at the same time and/or at different times. Moreover, they may be administered together in a single pharmaceutical composition or in separate pharmaceutical compositions.

The terms "treatment", "treating", and the like, refers to reversing, alleviating, or inhibiting the progress of the disease or condition to which such term applies, or one or more symptoms of such disease or condition. As used herein, these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound of the invention to a subject that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence of a disease or condition or of symptoms associated therewith.

"Abnormal cell growth", as used herein, refers to cell growth, either malignant (e.g. as in cancer) or benign, that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). Examples of benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis.

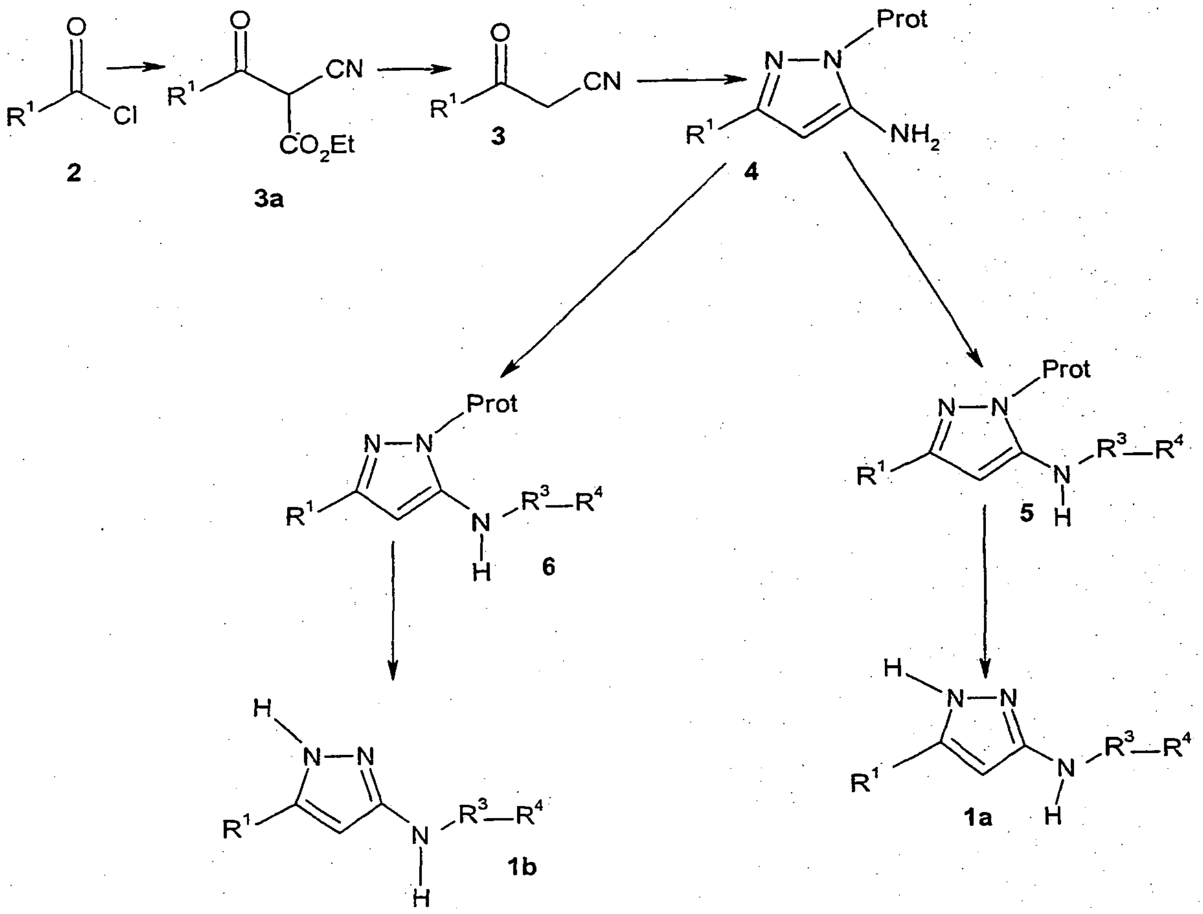
"Neurodegenerative diseases and conditions", as used herein and unless otherwise indicated, refers to diseases and conditions having associated therewith degeneration of neurons. Conditions and diseases that are neurodegenerative in nature are generally known to those of ordinary skill in the art.

References herein to diseases and conditions "the treatment of which can be effected or facilitated by altering dopamine mediated neurotransmission" mean a disease or condition that is at a temperature from about 21 °C to 200 °C, preferably from about 100 °C to 118 °C. Reaction of **3** in a reaction inert solvent, such as a lower alcohol, in the presence of a hydrazine at a reaction temperature of from about 0 °C to about 150 °C, where a temperature of from about 70 °C to about 85 °C is preferred, affords the corresponding product **4**. The hydrazine used may be anhydrous hydrazine or a hydrate form of hydrazine, or N-alkyl-hydrazine or N-acyl-hydrazine. Anhydrous hydrazine or an alkyl hydrazine, for example 4-methoxy-benzyl-hydrazine, are preferred.

Coupling of **4** with an aryl halide or heteroaryl halide to obtain an intermediate of formula **5**, wherein R^3 is $-(CR^{10}R^{11})_0-$ (a bond) can be accomplished by reaction of **4** in a reaction inert solvent, preferably toluene, at a reaction temperature of from about 21 °C to about 150 °C, preferably at about 100 °C to about 110 °C, in the presence of a palladium catalyst, a base, preferably cesium carbonate or sodium or potassium tert-butoxide, a ligand, where preferred ligands are 2,2'-bis(diphenylphosphino)-1,1'-binaphythyl, 2-(dicyclohexylphosphino)biphenyl, and 2-(di-tert-butylphosphino)biphenyl, and in the presence of the appropriate aryl halide or heteroaryl halide, where aryl bromides or chlorides and heteroaryl bromides or chlorides are preferred. The metal catalyst may be a palladium species, for example palladium chloride, palladium acetate, dichlorobis(acetonitrile)palladium, or derivatives thereof, wherein palladium acetate is preferred. Removal of the protecting group from **5** can be accomplished by reaction of **5** in a reaction inert solvent, preferably methylene chloride or no solvent, in the presence of an acid, wherein trifluoro acetic acid is preferred, at a reaction temperature from about 20 °C to about 100 °C, preferably from about 65 °C to about 75 °C, to yield **1a**, wherein R^3 represents a bond and R^4 is as defined above for compounds of formula **1**.

Coupling of **4** to yield N-acyl derivatives of the nature **6** (wherein R^3 is $-C(=O)(CR^{10}R^{11})_n-$) can be accomplished by reaction of **4** in a reaction inert solvent, preferably methylene chloride, pyridine, tetrahydrofuran, or diethyl ether, in the presence of an acid chloride $ClC(=O)(CH_2)_nR^4$, acid anhydride $R^4(CH_2)_nC(=O))_2O$, or an activated carboxylic acid derivative $XC(=O)(CH_2)_nR^4$ wherein X represents the activating group, and in the presence of a amine base, such as triethyl amine or diisopropylethyl amine, wherein tripropylphosphonic anhydride and triethylamine are a preferred combination, at a temperature of from about –78 °C to about 40 °C. The activated carboxylic acid derivative can be prepared from the carboxylic acid and known activating reagents such as polymer supported coupling agents or coupling agents such as, for instance, dicyclohexyl carbodiimide, carbonyl diimidazole, tripropylphosphonic anhydride, alkyl chloroformate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, or any

Scheme 1



Scheme 2 illustrates an alternative method suitable for preparing compounds of formula **1**. The method depicted in Scheme 2 is preferred when R^4 is an electron deficient aryl moiety, such as 4-nitrophenyl, or an electron deficient heteroaryl moiety. Reaction of a ketone having the general structure of **8**, wherein R^1 and R^2 are as defined above for compounds of formula **1**, in a reaction inert solvent, wherein tetrahydrofuran or diethyl ether are preferred as solvents, at a reaction temperature from about -116 °C to about 50 °C, preferably at about –78 °C to about -65 °C, in the presence of a base, a hindered amine base being preferred, and also in the presence of an isothiocyanate of the general formula **9**, wherein R^3 is a bond ($-(CR^{10}R^{11})_0-$) and R^4 is aryl or heteroaryl, affords **10**. Examples of hindered amine bases include lithium diisopropyl amide, potassium bis(trimethylsilyl) amide, lithium bis(trimethylsilyl) amide, and other such standard literature reagents. Treatment of **10** in a reaction inert solvent, a preferred solvent being a lower alcohol, in the presence of an acid, preferably acetic acid, at a reaction temperature of from about 21 °C to about 100 °C, hexafluorophosphate, or any other such standard literature reagents, in the presence of a trialkyl amine base, such as triethyl amine or diisopropylethyl amine, wherein tripropylphosphonic anhydride and triethylamine are a preferred combination.

Removal of the protecting group on **10b**, **10c**, or **10d** may be accomplished by reaction in a reaction inert solvent, wherein methylene chloride or no solvent is preferred, in the presence of an acid, preferably trifluoro acetic acid, at a reaction temperature from about 20 °C to about 100 °C, preferably from about 65 °C to about 75 °C, to yield the corresponding compounds of formula **1**, for example **1c**, as depicted in Scheme 2.

Scheme 3 illustrates an alternative method suitable for the preparation of compounds of formula **1**. The method illustrated in Scheme 3 is preferred when R^1 is substituted with R^5 selected from $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-C(=O)R^7$, $-C(=O)OR^7$, and $-C(=O)NR^7R^8$. Referring to Scheme 3, reacting an organolithium base, preferably *n*-butyl lithium, *sec*-butyl lithium, phenyl lithium, or *tert*-butyl lithium, at a reaction temperature from about -116 °C to about 50 °C, preferably at about –78 °C to about -45 °C, in a reaction inert solvent, especially tetrahydrofuran or diethyl ether, in the presence of alkylnitrile, preferably acetonitrile, and in the presence of an ester of the formula **11**, wherein R^1 is as defined above and R^5 is a protected oxo moiety (specifically a ketal or acetal) or R^5 is as defined above, gives **3b**, wherein R^5 is the same as in the compound of formula **11**. Processing of a compound with the formula **3b** to a compound with the formula **1d** or formula **1e** where R^3 is, respectively, $-C(=O)(R^{10}R^{11})_n-$ or a bond and R^5 is as in the compound of formula **11** can be accomplished as described in the description of Scheme 1. If R^5 is a protected oxo moiety, conversion of such group to carbonyl, can be accomplished at the same time as removal of the protecting group from the pyrazole nitrogen.

Alternatively, the amine of **4a** can be treated with a base, such as triethylamine, diisopropylethylamine, pyridine, or 2,6-lutidine, and a chloroformate $ClC(=O)OR^4$ (diisopropylethylamine and aryl or heteroarly chloroformates are a preferred combination) as described above for scheme 1 to afford a carbamate intermediate **7a** where R^3–C(=O)O- and R^4 is as defined above for compounds of formula **1**.

Subsequent treatment of **7a** formed in the preceding paragraph with a primary or secondary amine in a solvent such as dioxane, dimethylformamide, or acetonitrile, where a 1:1 mixture of dioxane: dimethylformamide is preferred, at a temperature between about 40 °C and about 90 °C, where about 70 °C is preferred, affords the corresponding urea intermediate **7b** where R^3 is $-C(=O)NR^9-$ and R^4 is as defined above for compounds of formula **1**.

Intermediate **7c** wherein R^3 is $-(CR^{10}R^{11})_{(1-3)}-$ can be prepared from intermediate **4a** by reaction of **4a** with an oxo moiety (aldehyde or ketone) in a reaction inert solvent, preferably toluene, tetrahydrofuran or methanol at a reaction temperature from about 0 °C to about 110 °C, preferably about 21 °C, in the presence of a reducing reagent, where preferred reducing reagents are sodium triacetoxyborohydride, sodium cyanoborohydride, and lithium aluminum hydride to afford an intermediate of formula **6a** wherein R^3 is $-(CR^{10}R^{11})_{(1-3)}-$. Removal of the protecting group from this intermediate **6a** can be achieved as described, i.e. in a reaction inert solvent, wherein trifluoro acetic acid is preferred, at a reaction temperature from about 20 °C to about 100 °C, preferably from about 65 °C to about 75 °C.

°C, where from about –78 °C to about -40 °C are preferred, to afford a compounds of formula 1 where R^5 –$NR^7C(=O)OR^8$. Subsequent treatment of the carbamate of the formula **1** with a primary or secondary amine in a solvent such as dioxane, dimethylformamide, or acetonitrile, where a 1:1 mixture of dioxane: dimethylformamide is preferred, at a temperature between 40 °C and 90 °C, where 70 °C is preferred, affords the corresponding urea intermediate where R^5 is –$NR^7C(=O)NR^8R^9$.

Removal of the protecting group on **12**, **13**, **14**, **15**, **16**, or **17** or any of the analogous compounds described above wherein R^3 and/or R^5 is instead –$C(=O)O$-, –$C(=O)NR^9$-, or –$(CR^{10}R^{11})_{(1-3)}$- *may be accomplished by reaction in a reaction inert solvent*, wherein methylene chloride or no solvent is preferred, in the presence of an acid, wherein trifluoro acetic acid is preferred, at a reaction temperature from about 20 °C to about 100 °C, preferably from about 65 °C to about 75 °C, affording respective compounds of formula **1**, for example a compound formula **1c**, wherein R^3 is a bond and R^5 is -$NR^7C(=O)R^8$ or a compound of formula **1f**, wherein R^3 is –$C(=O)(CR^{10}R^{11})_n$- and R^5 is -$NR^7C(=O)R^8$.

Conversion of the oxo (=O) moiety to a hydroxyl moiety (-OH), as in **18** and **23**, can be accomplished using well-established chemistry. The preferred method is by reaction of **12** or **15** or intermediate analogous thereto in a reaction inert solvent, preferably a tetrahydrofuran/water mixture, at a reaction temperature from about –78 °C to about 50 °C, preferable at about 20 °C, in the presence of a reducing agent, preferably $NaBH_4$ or lithium aluminum hydride, to afford **18** or **23** or compound analogous thereto wherein R^3 is –C(=O)O-, –C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$-.

Reaction of **18** or **23** or compound analogous thereto wherein R^3 is –C(=O)O-, -C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$- in a reaction inert solvent, preferably tetrahydrofuran, at a reaction temperature from about –20 °C to about 50 °C, preferably at about 20 °C, in the presence of R^7-halide, where the preferred R^7-halide is R^7-Cl, affords **19** or **24** or compound analogous thereto wherein R^3 is –C(=O)O-, -C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$-, in each case R^5 being -OR^7. Removal of the protecting group can be accomplished by reaction in a reaction inert solvent, wherein methylene chloride or no solvent is preferred, in the presents of an acid, wherein trifluoro acetic acid is preferred, at a reaction temperature from about 20 °C to 100 °C, preferably from about 65 °C to about 75 °C, to obtain a compound of formula **1g**, wherein R^3 is a bond and where R^5 = OR^7, a compound of formula **1h**, wherein R^3 is -C(=O)(CR^{10}R^{11})$_{(0-3)}$-, or an analogous compound wherein R^3 is –C(=O)O-, –C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$-.

Alternatively, treatment of a solution of compound **12** or **15** or analogous intermediate wherein R^3 is –C(=O)O-, -C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$- (in each case R^5 being an oxo moiety, specifically carbonyl) in a reaction inert solvent, where tetrahydrofuran is preferred, with an organometallic reagent, such as an organomagnesium halide, organolithium, organocerium, organotitanium, organozinc, organocopper, or organoaluminum, where the organomagnesium halide (Grignard reagent) or organolithium reagents are preferred, at a temperature from about –78 °C to about 40 °C, where –78 °C to about 0 °C is preferred, affords the alcohol product **21** or **26** or analogous compound wherein R^3 is –C(=O)O-, -C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$-, wherein in each case R^1 is hydroxylated and substituted with R^7, for example (5-(3-hydroxy, 3-phenyl-cyclobutyl)-2-(Prot)-pyrazol-3-yl)-naphthalen-2-yl-amine. Removal of the alcohol is accomplished by reaction of **21** or **26** or analogous compound in an inert solvent, such as methylene chloride, chloroform, or 1,2-dichloroethane, or preferably no solvent, in the presence of an acid, preferably trifluoroacetic acid, and in the presence of a silane, where triethylsilane and triphenylsilane are preferred, at a temperature from about –10 °C to about 50 °C, where about 20 °C to about 40 °C is preferred, obtaining a compound of formula **22** or **27** or compound analogous thereto but wherein R^3 is –C(=O)O-, –C(=O)NR^9-, or –(CR^{10}R^{11})$_{(1-3)}$-, the intermediate in each case comprising R^7 bonded directly to R^1.

about 65 °C to about 75 °C, affording a compound of formula **1i**, **1k**, or other compound of formula **1**.

Compounds of formula **1** as described herein wherein R^2 is other than hydrogen can be prepared by transformations of the compounds of formula **1** herein wherein R^2 is hydrogen using methods that are well known in the art. For example, referring to Scheme 3, *supra*, compounds of formula **1** wherein R^2 is F can be prepared by treating compounds of formula 17, 6a, or 14 with N-fluorobenzenesulfonimide in a reaction of inert solvent, wherein toluene, dioxane, or xylenes are preferred, from about room temperature to about 150°C, preferably from about 100°C to about 120°C to obtain the corresponding intermediates wherein R^2 is F. Removal of the protecting group from these intermediates may be accomplished by reaction in a reaction of inert solvent, wherein methylene chloride or no solvent are preferred, in the presence of an acid, wherein trifluoro acetic acid is preferred, at a reaction temperature from about 20°C to about 100°C, preferably from about 65°C to about 75°C, thus affording compounds of formula **1** wherein R^2 is F.

Some of the compounds of formula **1** prepared according to the above processes are obtained as a mixture of isomers or enantiomers. Such mixtures of isomers or enantiomers are within the scope of the present invention. The separation of such mixtures into the single isomers or enantiomers according to conventional techniques is also within the scope of the present invention, as are the separated isomers and enantiomers themselves.

Pharmaceutically acceptable salts of a compound of formula **1** can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base or acid with one chemical equivalent of a pharmaceutically acceptable acid or base. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids. Illustrative bases are sodium, potassium, and calcium.

A compound of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining a compound of formula **1** or a pharmaceutically acceptable salt thereof can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing a compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or

European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

(R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California). These and other VEGF inhibitors can be used in the present invention as described herein.

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), can also be combined with a compound of formula **1**, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with a compound of formula **1**, in accordance with the present invention.

A compound of formula **1**, can also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as farnesyl protein transferase inhibitors. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

reference. The compounds described in said references having NK-1 receptor antagonizing activity can be used in the present invention. However, other NK-1 receptor antagonists can also be used in this invention.

The effective amount of an NK-1 receptor antagonist in combination with a compound of formula **1** can generally be determined by a person of ordinary skill. A proposed effective daily dose range for an NK-1 receptor antagonist in combination with a compound of formula **1** is from about 0.07 to about 21 mg/kg body weight. The effective amount of the compound of formula **1** will be between about 0.0001 to about 10 mg/kg body weight. In some instances the amount of NK-1 receptor antagonist and/or the amount of the compound of formula **1** in the combination may be less than would be required on an individual basis to achieve the same desired effect in treating depression or anxiety.

The subject invention also provides combining a compound of formula **1** with a $5HT_{1D}$ receptor antagonist for treatment of depression or anxiety. A $5HT_{1D}$ receptor antagonist, as recited herein, is a substance that antagonizes the $5HT_{1D}$ subtype of serotonin receptor. Any such substance can be used in the present invention as described above in combination with a compound of formula **1**. Substances having $5HT_{1D}$ receptor antagonizing activity can be determined by those of ordinary skill in the art. For example, $5HT_{1D}$ receptor antagonists are described in WO 98/14433 (International Publication Date April 9, 1998); WO 97/36867 (International Publication Date October 9, 1997); WO 94/21619 (International Publication Date September 29, 1994); United States Patent 5,510,350 (issued April 23, 1996); United States Patent 5,358,948 (issued October 25, 1994); and GB 2276162 A (published September 21, 1994). These $5HT_{1D}$ receptor antagonists, as well as others, can be used in the present invention. The aforementioned published patent applications and patents are incorporated herein by reference in their entireties.

The effective amount of a $5HT1_D$ receptor antagonist in combination with a compound of formula **1** can generally be determined by a person of ordinary skill. A proposed effective daily dose range for a $5HT1_D$ receptor antagonist in combination with a compound of formula **1** is from about 0.01 to about 40 mg/kg body weight. The effective daily amount of the compound of formula **1** generally will be between about 0.0001 to about 10 mg/kg body weight. In some instances the amount of $5HT1_D$ receptor antagonist and/or the amount of compound of formula **1** in the combination may be less than would be required on an individual basis to achieve the same desired effect in treating depression or anxiety.

This invention also provides a pharmaceutical composition and method for treating depression or anxiety in a mammal comprising a compound of formula **1** and a SSRI. Examples of SSRIs that can be combined in a method or pharmaceutical composition with compounds of formula **1** and their pharmaceutically acceptable salts include, but are not instances, the amount of the antipsychotic and/or the amount of the compound of formula **1** in the combination may be less than would be required on an individual basis to achieve the same desired effect in treating depression or anxiety. It is furthermore to be understood that the present invention also encompasses combining a compound of formula **1** with antipsychotic or dopaminergic other than those in the aforementioned list.

A proposed amount for sonepiprazole in the above-described combination with a compound of formula **1**, is from about 0.005 to about 50 mg/kg body weight of the patient per day. A proposed amount of RP 62203 in such combination is from about 0.20 to about 6 mg/kg body weight of the patient per day. A proposed amount of NGD 941 in such combination is from about 0.1 to about 140 mg/kg of body weight per day. A proposed amount of balaperidone in such combination is from about 1 to about 100 mg/kg body weight per day. A proposed amount of flesinoxan in such combination is from about 0.02 to about 1.6 mg/kg body weight per day. A proposed amount for gepirone in such combination is from about .01 to about 2 mg/kg body weight per day. A proposed amount of L-745870 in such combination is from about 0.01 to about 250 mg/kg body weight per day, preferably from about 0.05 to about 100 mg/kg body weight per day. A proposed amount of risperidone in such combination is from about 0.05 to about 50 mg/kg body weight per day. A proposed amount of olanzapine in such combination is from about 0.0005 to about 0.6 mg/kg body weight per day. A proposed amount of ziprasidone in such combination is from about 0.05 to about 10 mg/kg body weight per day. In some instances for each of the aforementioned combinations, however, the amount of each specific ingredient in the combination may be less than would be required on an individual basis to achieve the same desired effect in treating a psychotic condition.

This invention also provides a pharmaceutical composition and method for treating Alzheimer's disease, mild cognitive impairment, or age-related cognitive decline comprising a compound of formula **1** and an acetylcholinesterase inhibitor. Acetylcholinesterase inhibitors are known in the art, and any such acetylcholinesterase inhibitor can be used in the above-described pharmaceutical composition or method. Examples of acetylcholinesterase inhibitors that can be used in this invention are ARICEPT (donepezil; U.S. Patent 4,895,841); EXELON (rivastigmine ((S)-[N-ethyl-3-[1-(dimethylamino)ethyl]phenyl carbamate); U.S. Patent 5,603,176 and U.S. Patent 4,948,807); metrifonate ((2,2,2-trichloro-1-hydroxyethyl)phosphonic acid dimethyl ester; U.S. Patent 2,701,225 and U.S. Patent 4,950,658); galantamine (U.S. Patent 4,663,318); physostigmine (Forest, USA); tacrine (1,2,3,4-tetrahydro-9-acridinamine; U.S. Patent 4,816,456); huperzine A (5R-(5α,9β,11E))-5-amino-11-ethylidene-5,6,9,10-tetrahydro-7-methyl-5,9-methaneocycloocta(b)pyridin-2-(1H)-one); and icopezil (5,7-dihydro-3-(2-(1-(phenylmethyl)-4-piperidinyl)ethyl)-6H-pyrrolo(3,2-f)-1,2-benzisoxazol-6-one; U.S. Patent

the amount of the compound of formula **1** in the combination may be less than would be required on an individual basis to achieve the same desired effect in treating said disorders.

The subject invention also provides for combining a compound of formula **1** with certain substances capable of treating a stroke or traumatic brain injury, such as TPA, NIF, or potassium channel modulators, for example BMS-204352. Such combinations are useful for treating neurodegenerative disorders such as stroke, spinal cord trauma, traumatic brain injury, multiinfarct dementia, epilepsy, pain, Alzheimer's disease, and senile dementia, for example.

For the above-described combination therapies and pharmaceutical compositions, the effective amounts of the compound of the invention and of the other agent can generally be determined by those of ordinary skill in the art, based on the effective amounts for the compounds described herein and those known or described for the other agent known in the art, for example the amounts described in the above-recited patents and patent application incorporated herein. The formulations and routes of administration for such therapies and compositions can be based on the information described herein for compositions and therapies comprising a compound of the invention as the sole active agent and on information provided for the other agent in combination therewith.

A specific compound of formula **1** can be determined to inhibit cdk2, cdk5, or GSK-3 using biological assays known to those of ordinary skill in the art, for example the assays described below.

The specific activity of a compound of formula **1** for inhibition of cdk5 or cdk2 can, for example, be ascertained by means of the following assays using materials available to those of ordinary skill in the art:

Enzyme activities can be assayed as the incorporation of [33P] from the gamma phosphate of [33P]ATP (Amersham, cat. no. AH-9968) into biotinylated peptide substrate PKTPKKAKKL. In such an assay, reactions are carried out in a buffer containing 50mM Tris-HCl, pH 8.0; 10mM MgCl2, 0.1mM Na3VO4, and 1mM DTT. The final concentration of ATP is about 0.5uM (final specific radioactivity of 4uCi/nmol), and the final concentration of substrate 0.75uM. Reactions, initiated by the addition of either cdk5 and activator protein p25 or cdk2 and activator cyclin E, may be carried out at room temperature for about 60 minutes. Reactions are stopped by addition of 0.6 volume of buffer containing (final concentrations): 2.5mM EDTA, 0.05%Triton-X 100, 100uM ATP, and 1.25 mg/ml streptavidin coated SPA beads (Amersham cat. no. RPNQ0007). Radioactivity associated with the beads is quantified by scintillation counting.

The specific activity of a compound of formula **1** for inhibition of GSK-3 can be determined in both cell-fee and cell-based assays, both of which are described in the art (see, The following Examples illustrate the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following Examples.

In the following Examples "TFA" indicates "trifluoroacetic acid", "THF" indicates "tetrahydrofuran", "MPLC" indicates "medium pressure liquid chromatography", "TLC" indicates "thin layer chromatography", "KOBu^{t}" indicates "potassium-*t*-butoxide", "DMSO" is "dimethyl sulfoxide", and "EtOAc" is "ethyl acetate". "MS", as in, for example, "Powdered 4 Å MS" is "molecular sieve".

EXAMPLES

Example 1. (5-Cyclobutyl-1H-pyrazol-3-yl)-(4-nitro-phenyl)-amine

Step 1. 3-Cyclobutyl-N-(4-nitro-phenyl)-3-oxo-thiopropionamide

To a stirring solution of lithium bis(trimethylsilyl)amide (3.6 mL, 3.6 mmol, 1.0 M in tetrahydrofuran) in tetrahydrofuran at –78 °C (acetone/CO_2 bath) was added a solution of methyl cyclobutyl ketone (400 uL, 360 mg, 3.6 mmol) in 10 mL of tetrahydrofuran. After 1 hr 4-nitro-phenyl isothiocyanate (328 mg, 1.8 mmol) was added in one portion. The reactant was allowed to slowly warm to rt overnight. After 16 hr the reaction was quenched with NH_4Cl, diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of this material was accomplished by MPLC using the Biotage Flash system eluting with a gradient of hexanes through 50 % EtOAc/ hexanes. The product-containing fractions were collected and concentrated to give 3-cyclobutyl-N-(4-nitro-phenyl)-3-oxo-thiopropionamide (266 mg, 53 % yield) as a yellow oil. R_f = 0.54 (30% acetone/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35-1.80 (m, 6H), 3.41 (dddd, J=8.2, 8.2, 7.9, 7.9 Hz, 1H), 4.04 (s, 2H), 7.70 (d, 8.7 Hz, 1H), 8.11 (d, 9.1 Hz. 2H), 8.23 (d, 9.2 Hz, 2H); LRMS *m/z* (APCI$^+$) 279 (M+1).

Step 2

To a stirring solution of 3-Cyclobutyl-N-(4-nitro-phenyl)-3-oxo-thiopropionamide from Step 1 (266 mg, 0.95 mmol) in 2 mL of EtOH was added 150 uL of acetic acid follow by anhydrous hydrazine (283 uL, 306 mg, 9.6 mmol). The reaction was heated to 71 °C for 2 hr and then cooled to rt. The reaction was then quenched with aqueous $NaHCO_3$ diluted with EtOAc and then the layers were separated. The organic layer was washed with water and the aqueous layer was back extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of this material was accomplished by MP LC using the Biotage Flash system eluting with a gradient of hexanes through 50 % acetone/ hexanes. The product containing fractions were collected and concentrated to give (5-cyclobutyl-1H-pyrazol-3-yl)-(4-nitro-phenyl)-amine (216 mg, 88%) as a tan solid. R_f 0.36 (30% acetone/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-2.22 (m, 4H),

^{1}HNMR (400MHz, CDCl$_3$), δ 1.85-2.15 (m, 4H), 2.26-2.32 (m, 2H), 3.39 (dddd, J=8.7, 8.7, 8.3, 8.3Hz, 1H), 4.29 (s, 2H), 5.41 (s, 1H), 5.80 (bs, 2H), 7.26 (7.31 (m, 4H). LRMS *m/z* (APCI$^+$) 262.3 (M+1).

Example 7. (3-Bromo-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine

The title compound was prepared according to the method for Example 1, using analogous reactants.

^{1}HNMR (400MHz, CDCl$_3$), δ 1.82-1.99 (m, 2H), 2.06-2.17 (m, 2H), 2.21-2.29 (m, 2H), 3.39 (dddd, J=8.8, 8.8, 8.8, 8.8Hz, 1H), 5.86 (s, 1H), 6.78 (bs, 1H), 6.98-6.92 (m, 2H), 7.04 (dd, J=7.9, 7.8Hz, 1H), 7.24 (s, 1H), 9.80 (bs, 1H). LRMS *m/z* (APCI$^+$) 292.3, 294.2 (M+1).

Example 8. [5-(1,4-Dioxa-spiro[4.4]non-7-yl)-1H-pyrazol-3-yl]-(3-trifluoromethyl-phenyl)-amine

The title compound was prepared according to the method for Example 1, using analogous reactants.

^{1}HNMR (400MHz, CDCl$_3$), δ 1.72-2.16 (m, 5H), 2.25 (ddd, J=13.7, 8.7, 0 Hz, 1H), 3.26 (dddd, J=8.3, 8.2, 8.2, 7.8Hz, 1H), 3.91-3.97 (m, 4H), 5.83 (s, 1H), 6.71 (bs, 1H), 7.06-7.32 (m, 4H), 9.0 (bs, 1H). LRMS *m/z* (APCI$^+$) 354.1 (M+1).

Example 9. (2-Chloro-4-nitro-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine

The title compound was prepared according to the method for Example 1, using analogous reactants.

R$_f$ 0.35 (30% EtOAc/Hexane), ^{1}H NMR (400MHz, CDCl$_3$), δ 1.90-2.23 (m, 4H), 2.36-2.44 (m, 2H), 3.48-3.57 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 5.96 (s, 1H), 7.72-7.76 (d, 1H), 8.05-8.08 (d, 1H), 8.26 (s, 1H). LRMS *m/z* (APCI$^+$) 293 (M+1).

Example 10. (3,5-Bis-trifluoromethyl-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine

The title compound was prepared according to the method for Example 1, using analogous reactants.

R$_f$ 0.35 (30% EtOAc/Hexane), ^{1}H NMR (400MHz, CDCl$_3$), δ 1.80-2.21 (m, 4H), 2.31-2.40 (m, 2H), 3.47-3.51 (dddd, J=8.7, 8.7, 8.7, 8.7Hz, 1H), 5.83 (s, 1H), 7.26 (s, 1H), 7.56 (s, 1H), 7.56 (s, 1H). LRMS *m/z* (APCI$^+$) 350 (M+1).

Example 11. 4-(5-Cyclobutyl-2H-pyrazol-3-ylamino)-benzonitrile

The title compound was prepared according to the method for Example 1, using analogous reactants.

R$_f$ 0.38 (50% EtOAc/ Hexane), ^{1}H NMR (400 MHz, CD$_3$OD), δ 1.88-2.11 (m, 2H), 2.15-2.25 (m, 2H), 2.32-2.40 (m, 2H), 3.49-3.57 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 5.85 (s, 1H), 7.22-7.25 (dd, J=2.5 Hz, 2H), 7.46-7.49 (dd, J=2.5 Hz, 2H). LRMS *m/z* (APCI$^+$) 239

Preparation 2.1. 2-Cyano-3-oxo-pentanoic acid ethyl ester

The title compound was prepared according to the method for Preparation 1.1, using analogous reactants.

^{1}H NMR (400MHz, $CDCl_3$), δ 1.23-1.27 (t, 3H), 1.34-1.37 (t, 3H), 2.61-2.66 (q, 2H), 4.30-4.35 (q, 2H), 13.70 (s, 1H). LRMS *m/z* ($APCI^-$) 168 (M-1).

Preparation 1.2. 3-Cyclobutyl-3-oxo-propionitrile

To 2-cyano-3-cyclobutyl-3-oxo-propionic acid ethyl ester (Preparation 1.1) in 40 mL of DMSO was added 2 mL of H_2O and then the reaction was heated to 118 °C. After 35 min the reaction was cooled in an ice water bath and then quenched with a saturated solution of NaCl. This reaction mixture was further diluted with H_2O and CH_2Cl_2 and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound of Preparation 1.2 as a yellow oil. This material was used without further purification.

^{1}H NMR (400MHz, $CDCl_3$), δ 1.83-2.17 (m, 2H), 2.19-2.30 (m, 2H), 2.31-2.55 (m, 2H), 3.39 (s, 2H), 3.39-3.43 (dddd, J=8.5, 8.5, 8.5, 8.5Hz, 1H). LRMS *m/z* ($APCI^-$) 122 (M-1).

Preparation 1.3. 5-Cyclobutyl-2-(4-methoxy-benzyl)-2H-pyrazol-3-ylamine

To crude 3-cyclobutyl-3-oxo-propionitrile prepared above in 515 mL of EtOH was added 4-methoxy-benzyl-hydrazine (12.6 g, 82.9 mmol) and the reaction was heated to reflux (oil bath at 85 ° C). After 2 hr the reaction was cooled to rt and concentrated under reduced pressure to give a viscous oil. Purified of this material was accomplished by MPLC using the Biotage Flash 45S system eluting with a gradient of 10% and 20% EtOAc/ hexanes. The product containing fractions were collected and concentrated to give the title compound (10.2 g, 77% yield over 2 steps) as a colorless solid.

R_f 0.3 (40% EtOAc/Hexane), ^{1}H NMR (400MHz, $CDCl_3$), δ 1.85-2.00 (m, 2H), 2.12-2.20 (m, 2H), 2.25-2.31 (m, 2H), 3.41-3.46 (dddd, J=8.1, 8.1, 8.1, 8.1Hz, 1H), 3.76 (s, 3H), 5.07 (s, 2H), 5.46 (s, 1H), 6.82-6.84 (d, J=6.64 Hz, 2H), 7.07-7.09 (d, J=6.64 Hz, 2H). LRMS *m/z* ($APCI^+$) 258 (M+1).

Preparation 2.3. 5-Ethyl-2-(4-methoxy-benzyl)-2H-pyrazol-3-ylamine

The title compound was prepared according to the method for Preparation 1.3, using Preparation 2.1 instead of Preparation 1.1.

R_f 0.4 (50% EtOAc/Hexane, ^{1}H NMR (400MHz, $CDCl_3$), δ 1.16-1.20 (t, 3H), 2.49-2.55 (q, 2H), 3.74 (s, 3H), 5.05 (s, 2H), 5.36 (s, 1H), 6.80-6.82 (d, 2H), 7.06-7.08 (d, 2H). LRMS *m/z* ($APCI^+$) 232 (M+1).

Preparation 1.4. [5-Cyclobutyl-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-(6-methoxy-pyridin-2-yl)-amine

R_f 0.28 (25% EtOAc/Hexane), ^1H NMR (400MHz, $CDCl_3$), δ 1.22-1.26 (t, 3H), 2.60-2.66 (q, 2H), 3.74 (s, 3H), 3.82 (s, 3H), 5.12 (s, 2H), 6.01-6.02 (d, 1H), 6.04 (s, 1H), 6.16-6.18 (d, 1H), 6.79-6.81 (d, J=6.64 Hz, 2H), 7.07-7.09 (d, J=6.64 Hz, 2H), 7.32-7.36 (apt, 1H). LRMS *m/z* ($APCI^+$) 339 (M+1).

Example 15. (5-Cyclobutyl-2H-pyrazol-3-yl)-(3-methoxy-phenyl)-amine

To [5-Cyclobutyl-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-(3-methoxy-phenyl)-amine (Preparation 1.4, 120 mg, 0.331 mmol) was added neat trifluoro acetic acid (2.0 mL) and the reaction was heated to 70 °C. After 48 hr the reaction was cooled to rt and concentrated under reduced pressure. Purification of this material was accomplished by MPLC using the Biotage Flash system eluting with 40% EtOAc/hexanes. The product-containing fractions were collected and concentrated to give the title compound (30 mg, 37 % yield).

R_f 0.35 (75% EtOAc/Hexane), ^1H NMR (400MHz, $CDCl_3$), δ 1.80-2.03 (m, 2H), 2.12-2.17 (m, 2H), 2.29-2.33 (m, 2H), 3.40-3.48 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 3.77 (s, 3H), 5.88 (s, 1H), 6.41-6.43 (d, J=10.4 Hz, 1H), 6.65-6.68 (m, 1H), 6.71-6.72 (m, 1H), 7.11-7.15 (apt, 1H). LRMS *m/z* ($APCI^+$) 244 (M+1).

Example 16. (5-Cyclobutyl-2H-pyrazol-3-yl)-(6-trifluoromethyl-pyridin-2-yl)-amine

The title compound was made according to the method for Example 15, using analogous reactants.

R_f 0.50 (10% MeOH/CH_2Cl_2), ^1H NMR (400MHz, CD_3OD), δ 1.86-2.19 (m, 2H), 2.21-2.32 (m, 2H), 2.32-2.39 (m, 2H), 3.51-3.57 (dddd, J=8.7, 8.7, 8.7, 8.7Hz, 1H), 6.15 (s, 1H), 7.10 (d, J=9.13 Hz, 1H), 7.73-7.76 (d, J=8.72 Hz, 1H), 8.38 (s, 1H). LRMS *m/z* ($APCI^+$) 283 (M+1).

Example 17. (5-Cyclobutyl-2H-pyrazol-3-yl)-(3-trifluoromethyl-phenyl)-amine

The title compound was made according to the method for Example 15, using analogous reactants.

R_f 0.30 (40% EtOAc/Hexane), ^1H NMR (400MHz, $CDCl_3$), δ 1.92-2.26 (m, 4H), 2.38-2.46 (m, 2H), 3.50-3.58 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 6.01 (s, 1H), 7.31-7.47 (m, 4H). LRMS *m/z* ($APCI^+$) 282 (M+1).

Example 18. N-(5-Cyclobutyl-2H-pyrazol-3-yl)-N',N'-dimethyl-benzene-1,3-diamine

The title compound was made according to the method for Example 15, using analogous reactants.

R_f 0.50 (5% MeOH/CH_2Cl_2), ^1H NMR (400Mz, $CDCl_3$), δ 1.91-2.18 (m, 2H), 2.20-2.30 (m, 2H), 2.35-2.43 (m, 2H). 3.11 (s, 6H), 3.48-3.56 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 6.13

5.83 (s, 1H), 5.93 (d, J=8.31 Hz, 1H), 6.09 (d, J=7.89 Hz, 1H), 7.29-7.33 (1H, apt). LRMS *m/z* (APCI$^+$) 258 (M+1).

Example 24. (5-Ethyl-2H-pyrazol-3-yl)-(6-methoxy-pyridin-2-yl)-amine

The title compound was made according to the method for Example 15, using analogous reactants.

R$_f$ 0.20 (50% EtOAc/Hexane), ^{1}H NMR (400MHz, CDCl$_3$), δ 1.20-1.28 (m, 3H), 2.60-2.68 (m, 2H), 3.90- (s, 3H), 6.25-6.27 (d, 1H), 6.45-6.47 (d, 1H), 6.54 (s, 1H), 7.42-7.46 (apt, 1H). LRMS *m/z* (APCI$^+$) 219 (M+1).

Example 25. (5-Cyclobutyl-2H-pyrazol-3-yl)-(6-methoxy-pyridin-2-yl)-amine

The title compound was made according to the method for Example 15, using analogous reactants.

R$_f$ 0.30 (50%EtOAc/Hexane), ^{1}H NMR (400MHz, CDCl$_3$), δ 1.87-2.23 (m, 4H), 2.33-2.41 (m, 2H), 3.46-3.55 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 3.93 (s, 3H), 6.26-6.28 (d, 1H), 6.46-6.47 (d, 1H), 6.57 (s, 1H), 7.43-7.47 (apt, 1H). LRMS *m/z* (APCI$^+$) 245 (M+1).

Preparation 3.1. 1,4-Dioxa-spiro[4.4]non-7-yl)-ethanone

To a stirring solution of known nitrile (1.25 g, 8.17g)((Aust. J. Chem. 1994, 47, 1833) in tetrahydrofuran at rt was added a solution of methyl magnesium bromide (5.4 mL, 16.3 mmol, 3.0M in THF) followed by copper (I) bromide (23 mg, 0,16 mmol). The reaction was then heated to 65 °C. After 20 hr the reaction cooled to rt and then to 0 °C (ice/water bath) and quenched with a saturated solution of NH$_4$Cl. This mixture was diluted with methylene chloride (100 mL) and the layers separated. The aqueous layer was extracted with methylene chloride (100 mL) and the combined organic layers were dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification was accomplished by vacuum distillation (120 °C, 2 mm) to give the title compound (1.39 g, 51% yield) as a clear colorless oil.

^{1}HNMR (400MHz, CDCl$_3$), δ 1.79-2.08 (m, 6H), 2.15 (s, 3H), 2.99 (dddd, J=8.3Hz, 1H), 3.87-3.94 (m, 4H). LRMS *m/z* (APCI$^+$) 171 (M+1).

Preparation 3.2. 3-(1,4-Dioxa-spiro[4.4]non-7-yl)-3-oxo-N-(3-trifluoromethyl-phenyl)-thiopropionamide

To a stirring solution of LiHMDS(3.2 mL, 3.2 mmol 1 M in THF) in 20 mL of THF at -78 °C (acetone/CO$_2$) was a precooled solution (–78 °C) of 1-(1,4-Dioxa-spiro[4.4]non-7-yl)-ethanone (Preparation 3.1, 500 mg, 2.94 mmol in 5 mL of THF) via cannula down the side of the flask. After 30 minutes, 1-isothiocyanato-3-trifluoromethyl-benzene (988 uL, 1.3 g, 6.5 mmol) was added dropwise via syringe. The resulting reaction was slowly allowed to warm to rt overnight. The reaction was then quenched with NaHCO$_3$, diluted with EtOAc and the layers were separated. Purification of this material was accomplished by MPLC using the

3.76 (s, 3H), 5.11 (s, 2H), 5.94 (s, 1H), 6.79-6.88 (m, 4H), 7.04-7.10 (m, 3H), 7.25-7.29 (m, 1H). LRMS *m/z* (APCI$^+$) 430 (M+1).

Example 26. 3-*Trans*-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentanone

The title compound was prepared according to the method for Preparation 3.4, using hydrazine instead of 4-methoxy-benzyl-hydrazine (see synthesis of Preparation 3.3, *supra*).

^{1}HNMR (400MHz, $CDCl_3$), δ 1.94-1.99 (m, 1H), 2.20-2.48 (m, 4H). 2.62 (ddd, J=18.2, 7.9, 0Hz, 1H), 3.38 (dddd, J=9.5, 9.5, 7.5, 6.6Hz, 1H), 5.85 (s, 1H), 7.09 (d, J=7.4Hz, 1H), 7.20 (d, J=8.3Hz, 1H), 7.26-7.33 (m, 2H). LRMS *m/z* (APCI$^+$) 310.3 (M+1).

Preparation 3.5. {2-(4-Methoxy-benzyl)-5-[3-(4-methoxy-benzylamino)-cyclopentyl]-2H-pyrazol-3-yl}-(3-trifluoromethyl-phenyl)-amine

To a stirring slurry of 3-[1-(4-Methoxy-benzyl)-5-(3-trifluoromethyl-phenylamino)-1H-pyrazol-3-yl]-cyclopentanone (Preparation 3.4, 3.3 g, 7.6 mmol) in 76 mL of toluene was added, powdered 4 Å MS (16.1 g), followed by 4-methoxybenzyl amine (2.0 g, 15.3 mmol). The resulting mixture was heated to 110 °C overnight. After 12 hr the reaction was cooled to rt and $Na(OAc)_3BH$ (3.2g, 15.3 mmol) was added and stirred for an additional hr before 4 Å MS were filtered off and the resulting solution was concentrated under reduced pressure. Purification of this material was accomplished by MPLC using the Biotage Flash 75S system eluting with a gradient of 5% through 8% $MeOH/CH_2Cl_2$ containing 0.1% NH_4OH. The product-containing fraction was collected and concentrated under reduced pressure to give the title compound (3.9 g, 92% yield) as a yellow viscous oil and a 3:1 mixture of diastereomers.

R_f 0.28 (8% $MeOH/CH_2Cl_2$), 3:2 ratio of *cis*, *trans* isomers seen in the ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 551 (M+1).

Examples 27 and 28. Isomers of [5-(3-Benzylamino-cyclopentyl)-1H-pyrazol-3-yl]-(3-trifluoromethyl-phenyl)-amine

A racemate comprising cis:trans isomers of [5-(3-Benzylamino-cyclopentyl)-1H-pyrazol-3-yl]-(3-trifluoromethyl-phenyl)-amine was prepared according to the method for Preparation 3.5, using Example 26 instead of Preparation 3.4. Cis:trans isomers (Examples 27 and 28) were isolated from the mixture by MPLC using the Biotage flash 755 system eluting with a gradient of 5% through 8% $MeOH/CH_2Cl_2$ containing 0.1% NH_4OH.

Example 27.

^{1}HNMR (400MHz, CD_3COCD_3), δ 1.65-1.79 (m, 1H), 1.81-2.07 (m, 4H), 2.25 (m, 1H), 2.50 (dddd, J=7.1, 7.1, 7.1, 7.1Hz, 1H), 3.24 (dddd, J=2.1, 2.1, 2.1, 2.1Hz, 1H), 3.80 (s, 2H), 5.70 (s, 1H), 7.01 (d, J=4.3Hz, 1H), 7.22-7.55 (m, 5H), 7.56 (d, J=2.1Hz, 1H), 7.98 (s, 1H), 8.01 (s, 1H). LRMS *m/z* (APCI$^+$) 401.3 (M+1).

two steps).

Rf 0.30 (55 MeOH/CH_2Cl_2); ^{1}HNMR (400MHz, CD_3COCD_3), δ 1.55-1.59 (m, 1H), 1.66-1.74 (m, 1H), 1.83 (s, 3H), 1.97-2.03 (m, 2H), 2.09-2.20 (m, 2H), 3.32 (dddd, J=8.3, 8.3, 8.3, 8.3Hz, 1H), 4.33 (dddd, J=12.9, 7.0, 7.0, 7.0Hz, 1H), 5.71 (s, 1H), 7.01 (d, J=7.9Hz, 1H), 7.16 (bs, 1H), 7.36 (dd, J=7.9, 7.9Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 7.99 (bs, 1H), 8.01 (bs, 1H). LRMS *m/z* (APCI$^+$) 353.2 (M+1).

Example 31. Pyridine-2-carboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide

The title compound was prepared according to the method for Example 30, using analogous reactants.

R_f 0.33 (5% MeOH/ CH_2Cl_2), 1:1 ratio of *cis, trans* isomers seen in ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 416 (M+1), mp 180.1 °C (HCl salt)

Example 32. Pyridine-2-carboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide

The title compound was prepared according to the method for Example 30, using analogous reactants.

R_f 0.28 (5% MeOH/ CH_2Cl_2), 1:1 ratio of *cis, trans* isomers seen in ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 483 (M+1), mp 162.5 °C (HCl salt)

Example 33. Cyclobutanecarboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide

The title compound was prepared according to the method for Example 30, using analogous reactants.

R_f 0.25 (5% MeOH/ CH_2Cl_2), 1:1 ratio of *cis, trans* isomers seen in ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 393 (M+1), mp 232.4 °C (HCl salt)

Example 34. 2,2-Dimethyl-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-propionamide

The title compound was prepared according to the method for Example 30, using analogous reactants.

R_f 0.23 (5% MeOH/ CH_2Cl_2), 1:1 ratio of *cis, trans* isomers seen in ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 395 (M+1), mp 249.2 °C (HCl salt)

Example 35. 4-Fluoro-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-benzamide

The title compound was prepared according to the method for Example 30, using analogous reactants.

R_f 0.30 (5% MeOH/ CH_2Cl_2), 1:1 ratio of *cis, trans* isomers seen in ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 433 (M+1); mp (dec) no distinct melting point.

pyrazol-3-ylamine

To crude (1,4-Dioxa-spiro[4.4]non-7-yl)-oxo-acetonitrile (Preparation 4.1) in EtOH (6.8 mL) was added 4-methoxy-benzyl-hydrazine (0.60 g, 4.0 mmol), and then the reaction was heated to 65 °C. After 2 1/2 hr the reaction was cooled to rt and concentrated under reduced pressure. Purification of this material was accomplished by MPLC using the Biotage Flash 40L system eluting with a gradient of 50% through 100% EtOAc/hexanes, collecting 18 mm fractions. The product containing-fraction was collected and concentrated under reduced pressure to give the title compound (0.83 g, 75% yield over 2 steps).

R_f 0.13 (50% EtOAc/hexanes); ^{1}HNMR (400MHz, $CDCl_3$), δ 2.10-1.72 (m, 5H), 2.23 (dd, J = 13.3, 7.9 Hz, 1H), 3.15 (dddd, J = 7.9, 7.9, 2.5, 2.5 Hz, 1H), 3.39 (br s, 2H), 3.73 (s, 3H), 3.91-3.84 (m, 4H), 5.03 (s, 2H), 5.34 (s, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 31.4, 36.4, 37.2, 43.1, 51.2, 55.5, 64.3, 64.5, 89.0, 114.4, 117.9, 128.3, 129.1, 145.2, 155.0, 159.3; LRMS *m/z* ($APCI^+$) 330 (M+1).

Preparation 4.3. N-[5-(1,4-Dioxa-spiro[4.4]non-7-yl)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide

To a stirring solution of 5-(1,4-Dioxa-spiro[4.4]non-7-yl)-2-(4-methoxy-benzyl)-2H-pyrazol-3-ylamine (Preparation 4.2, 0.83 g, 2.5 mmol) in CH_2Cl_2 (5 mL) was added a freshly prepared solution of naphthalen-1-yl-acetyl chloride (1.03 g, 5.0 mmol in CH_2Cl_2) followed by the addition of 1 mL of pyridine. After 2 hr, the reaction was quenched with H_2O, and 2 mL of a solution of NH_4OH (15%) was added. This mixture was diluted with CH_2Cl_2 and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of this material was accomplished by MPLC using the Biotage Flash 40L system eluting with a gradient of 25% through 50% acetone/hexanes, collecting 18 mm fractions. The product-containing fraction was collected and concentrated under reduced pressure to give the title compound (1.2 g, 97% yield) as a light yellow solid.

mp 162.8 °C; ^{1}HNMR (400MHz, $CDCl_3$), δ 2.09-173 (m, 5H), 2.21 (dd, J = 13.3, 7.9 Hz, 1H), 3.18 (dddd, J =7.5, 5.0 Hz, 1H), 3.68 (s, 3H), 3.89-3.81 (m, 4H), 3.98 (s, 2H), 4.60 (s, 2H), 6.22 (s, 1H), 6.36 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 8.7 Hz, 2H), 7.03 (br s, 1H), 7.23 (d, J = 6.7 Hz, 1H), 7.39 (dd, J = 7.1, 7.1 Hz, 1H), 7.53-7.45 (m, 2H), 7.88-7.83 (m, 2H), 7.89 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 31.2, 36.4, 37.2, 42.0, 42.9, 51.9, 55.4, 64.3, 64.5, 97.2, 114.2, 117.8, 123.7, 125.9, 126.7, 127.4, 127.7, 127.9, 128.7, 129.1, 129.32, 130.2, 132.1, 134.2, 135.3, 154.9, 159.2, 168.6; LRMS *m/z* ($APCI^+$) 498 (M+1).

Preparation 4.4. N-[2-(4-Methoxy-benzyl)-5-(3-oxo-cyclopentyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide

The title compound was synthesized according to the method for Preparation 3.4, using the title compound of Preparation 4.3 instead of the title compound of Preparation 3.3 as

Example 41. Cyclopropanecarboxylic acid {3-[5-(2-naphthalen-1-yl-acetylamino)-1H-pyrazol-3-yl]-cyclopentyl}-amide

The title compound was synthesized by the method for Example 30, using analogous reactants.

R_f 0.30 (5% MeOH/ CH_2Cl_2). 1:1 ratio of *cis*, *trans* isomers was seen in the ^{1}HNMR obtained in $CDCl_3$. LRMS *m/z* (APCI$^+$) 403 (M+1).

Example 42. 2-Naphthalen-1-yl-N-{5-[3-(2,2,2-trifluoro-acetylamino)-cyclopentyl]-2H-pyrazol-3-yl}-acetamide

The title compound was synthesized by the method for Example 30, using analogous reactants.

R_f 0.30 (5% MeOH/ CH_2Cl_2). 1:1 ratio of *cis*, *trans* isomers was seen in the ^{1}HNMR obtained in CD_3OD. LRMS *m/z* (APCI$^+$) 431 (M+1).

Example 43. N-{3-[5-(2-Naphthalen-1-yl-acetylamino)-1H-pyrazol-3-yl]-cyclopentyl}-benzamide

The title compound was synthesized by the method for Example 30, using analogous reactants.

R_f 0.30 (5% MeOH/ CH_2Cl_2). 1:1 ratio of *cis*, *trans* isomers was seen in the ^{1}HNMR obtained in $CDCl_3$. LRMS *m/z* (APCI$^+$) 439 (M+1).

The following title compounds of Examples 44-57 were synthesized by preparing an intermediate analogous to the title compound of Preparation 4.6, using the steps described in "Preparation 4.2" through "Preparation 4.5". In each case, a reactant analogous to naphthalen-1-yl acetal chloride used in synthesis of the title compound of Preparation 4.3 was used. This intermediate was than treated according to the method described for synthesis of the title compound of Example 30:

Example 44. 3-Methoxy-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide

R_f 0.33 (10% MeOH/CH_2Cl_2); mp 124.8 °C (mono HCl salt); ^{1}HNMR (400MHz, CD_3OD), δ 2.20 (dd, J = 10.2 Hz, 2H), 2.72-2.66 (m, 2H), 3.14 (apt quint, J= 8.8 Hz, 1H); 3.75 (s, 3H), 4.12 (s, 2H), 4.40 (apt quint, 8.4 Hz, 1H), 6.31 (s, 1H), 7.03-7.00 (m, 1H), 7.28 (dd, J = 7.8 Hz, 1H), 7.46-7.35 (m, 6H), 7.74 (d, J = 7.9 Hz, 1H), 7.81 (d, J=7.0 Hz, 1H), 8.01 (d, J= 7.4 Hz, 1H); ^{13}C NMR (100 Mz, CD_3OD) δ 170.6, 168.1, 160.0, 149.0, 146.0, 135.5, 134.2, 132.4, 131.3, 129.4, 128.6, 128.1, 127.9, 126.2, 125.7, 125.4, 123.7, 119.3, 117.3, 112.5, 93.8, 54.7, 41.5, 40.2, 36.9, 24.8; LRMS *m/z* (APCI$^+$) 455.1 (M+1).

Example 45. N-{*cis*-3-[5-(2-Naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-3-trifluoromethyl-benzamide

R_f 0.56 (10% MeOH/CH_2Cl_2); mp 142.8 °C (mono HCl salt); ^{1}HNMR (400MHz,

R_f 0.50 (10% MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, CD_3OD), δ 2.20-2.30 (m, 2H), 2.70-2.80 (m, 2H), 3.20 (apt quint, J=8.0Hz, 1H), 4.18 (s, 2H), 4.48 (apt quint, J=7.8Hz, 1H), 6.24 (bs, 1H), 7.38-7.50 (m, 7H), 7.75-7.88 (m, 4H), 8.00-8.05 (m, 1H). ^{13}C-NMR: 24.68, 36.92, 40.12, 41.47, 93.54, 123.68, 125.39, 125.72, 126.25, 127.20, 127.96, 128.12, 128.35, 128.59, 131.17, 131.56, 132.44, 134.20, 145.86, 149.19, 168.39, 170.60. MS LRMS *m/z* (APCI$^+$) 425 (M+1), mp 194.0 °C(HCl salt).

Example 50. 2-Cyclopropyl-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-acetamide

R_f 0.60 (10% MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, CD_3OD), δ 0.93 (t, J=7.5Hz, 2H), 1.34 (d, J=6.2Hz, 1H), 1.65 (d, J=5.0Hz, 1H), 1.70-1.78 (m, 2H), 2.01-2.15 (m, 2H), 2.55-2.58 (m, 1H), 2.62-2.68 (m, 2H), 3.20 (apt quint, J=7.8Hz, 1H), 4.20 (s, 2H), 5.40 (apt quint, J=6.2Hz, 1H), 6.22 (bs, 1H), 7.40-7.56 (m, 4H), 7.78-7.88 (m, 2H), 8.02-8.08 (m, 1H). ^{13}C-NMR: 8.27, 24.52, 26.64, 36.63, 36,85, 36.96, 39.47, 40.12, 40.77, 77.66, 93.27, 112.50, 123.67, 125.38, 125.73, 126.24, 127.95, 128.14, 128.59, 132.45, 134.21, 146.71, 169.62, 170.63. MS LRMS *m/z* (APCI$^+$) 403 (M+1), mp 93.2 °C (HCl salt).

Example 51. 6-Chloro-pyridine-2-carboxylic acid {*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide

R_f 0.50 (10% MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, CD_3OD), δ 2.25-2.42 (m, 2H), 2.76-2.82 (m, 2H), 3.30 (apt quint, J=7.9Hz, 1H), 4.22 (s, 2H), 4.54 (apt quint, J=7.5Hz, 1H), 6.35 (s, 1H); 7.42-7.64 (m, 5H), 7.81-7.89 (m, 2H), 7.93-8.11 (m, 3H). ^{13}C-NMR: 24.58, 36.65, 40.17, 41.06, 77.50, 93.77, 121.03, 122.58, 123.67, 123.82, 124.50, 125.40, 125.72, 126.24, 127.37, 128.01, 128.11, 128.59, 134.20, 140.63, 140.70, 144.41, 150.36, 170.70, 182.15. MS LRMS *m/z* (APCI$^+$) 460 (M+1), mp (dec) (HCl salt).

Example 52. Quinoline-2-carboxylic acid {*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide

R_f 0.30 (5% MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, CD_3OD), δ 2.25-2.38 (m, 2H), 2.76-2.78 (m, 2H), 3.25 (apt quint, J=8.3Hz, 1H), 4.16 (s, 2H), 4.56 (apt quint, 8.7Hz, 1H), 6.36 (bs, 1H), 7.38-7.49 (m, 4H), 7.60-7.64 (m, 1H), 7.71-7.99 (m, 4H), 8.02-8.13 (m, 3H), 8.36 (d, J=8.7Hz, 1H). ^{13}C-NMR: 24.80, 37.08, 40.22, 41.08, 53.50, 94.03, 118.41, 123.70, 124.50, 125.39, 125.70, 126.22, 127.25, 127.82, 128.15, 128.57, 129.42, 129.54, 130.34, 132.43, 134.18, 137.70, 137.80, 146.02, 146.73, 148.93, 149.60, 164.89, 170.57. MS LRMS *m/z* (APCI$^+$) 476 (M+1), mp 200.3 °C (HCl salt).

Example 53. Pyrazine-2-carboxylic acid {*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide

R_f 0.30 (5% MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, CD_3OD), δ 2.25-2.38 (m, 2H), 2.75-2.84 (m, 2H), 3.26 (apt quint, J=8.7Hz, 1H), 4.21 (s, 2H), 4.55 (apt quint, J=8.7Hz, 1H), 6.28

method for Example 30.

R_f 0.50 (10%MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, $CDCl_3$), δ 1.64 (d, J=6.6Hz, 3H), 4.12 (s, 2H), 5.97 (dd, J=6.6, 6.6Hz, 1H), 6.47 (s, 1H), 7.34-7.40 (m, 2H), 7.42-7.50 (m, 2H), 7.74-7.87 (m, 3H). LRMS *m/z* (APCI$^+$) 296 (M+1); mp 101.3 °C (HCl salt).

Example 59. N-[5-(2-Hydroxy-(1S)-methyl-ethyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide

Synthesis of the title compound was accomplished by the method for Preparation 4.3, using a reactant analogous to naphthalen-1-yl-acetyl chloride. This was followed by deprotection. The resulting intermediate was treated according to the method for Example 30.

^{1}HNMR (400MHz, CD_3OD), δ 1.25 (d, J=7.1Hz, 3H), 2.92-3.01 (m, 1H), 3.58-3.62 (m, 2H), 4.20 (bs, 2H), 6.22 (bs, 1H), 7.40-7.58 (m, 4H), 7.80 (d, J=7.0Hz, 1H), 7.88 (d, J=7.1Hz, 1H), 8.06 (d, J=7.0Hz, 1H). LRMS *m/z* (APCI$^+$) 310 (M+1), mp 117.6 °C (HCl salt).

Preparation 6.1. N-[5-[1-(Benzothiazol-2-yloxy)-ethyl]-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide

To a stirring solution of N-[5-(1-Hydroxy-ethyl)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide (300 mg, 0.72 mmol) in 7.2 mL of THF was added 2-chlorobenzthiozole (104 uL, 0.79 mmol, 135 mg) followed by a solution of $KOBu^t$ (1.4 mL, 1.4 mmol, 1.0 M in THF) dropwise. After 2 hrs the reaction was quenched with NH_4Cl and then diluted with EtOAc. The layers were separated and the organic layer was dried of $MgSO_4$, filtered and concentrated under reduced pressure. Purification of this material was accomplished by MPLC using a 10 g ISCO cartridge on a Biotage system eluting with 30% EtOAc/hexanes, collecting 8 mm fractions. The product-containing fraction was collected and concentrated under reduced pressure to give the title compound (100 mg, 25% yield) as a yellow viscous oil.

R_f 0.50 (50% EtOAc/Hexanes). ^{1}HNMR (400MHz, $CDCl_3$), δ 1.82 (d, J=7.5Hz, 3H), 3.74 (s, 3H), 4.06 (d, J=4.6Hz, 2H), 4.65 (dd, J=15.8, 15.8Hz, 2H), 6.02 (dd, J=7.1, 7.1Hz, 1H), 6.27 (s, 1H), 6.29 (d, J=8.7Hz, 2H), 6.51 (d, J=8.7Hz, 2H), 6.99-7.06 (m, 3H), 7.27-7.29 (m, 1H), 7.30-7.38 (m, 1H), 7.40-7.43 (m, 1H), 7.50-7.60 (m, 2H), 7.87-7.95 (m, 3H). LRMS *m/z* (APCI$^+$) 549 (M+1).

Example 60. N-{5-[(1S)-(Benzothiazol-2-yloxy)-ethyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide

The title compound was synthesized using Preparation 6.1 according to the method for Example 15.

R_f 0.41 (5% MeOH/ CH_2Cl_2). ^{1}HNMR (400MHz, $CDCl_3$), δ 1.81 (d, J=7.1Hz, 3H), 4.17 (s, 2H), 5.84 (dd, 6.7, 6.7Hz, 1H), 6.68 (s, 1H), 6.85 (d,J=7.9 Hz, 1H), 7.10-7.20 (m, 2H), 7.32-7.57 (m, 5H), 7.79-7.86 (m, 2H), 7.97-7.99 (m, 1H). LRMS *m/z* (APCI$^+$) 429 (M+1).

methanol) to afford 54 mg (80% yield) of the title comopund.

1H NMR (400 MHz, CDCl3) δ 7.9 (m, 3H), 7.55 (m, 4H), 7.46 (m, 1H), 7.35 (m, 3H), 7.21 (m, 1H), 6.90 (m, 1H), 6.80 (dd, *J* = 0.8, 8.7 Hz, 1H), 6.54 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 8.7 Hz, 2H), 6.34 (s, 1H), 4.65 (s, 2H), 4.12 (s, 2H), 3.74 (s, 3H), 3.20 (m, 1H), 3.01 (m, 2H), 2.55 (m, 2H); MS (AP/Cl): 518.2 (M+H)+.

Preparation 7.2 N-[2-(4-methoxy-benzyl)-5-(*cis*-3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide

A solution of N-[5-(3-hydroxy-3-phenyl-cyclobutyl)-2-(4-methoxy-benzyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide (Preparation 7.1, 54 mg, 0.10 mmol) in 1:1 methylene chloride–trifluoroacetic acid (4 mL) was treated with triethylsilane (1.2 mL) at 23 °C. After stirring for 16 h, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (100:1 chloroform–methanol) to afford 39 mg (78% yield) of the title compound as a 10:1 mixture of *cis* – *trans* isomers.

1H NMR (400 MHz, $CDCl_3$): δ 7.90 (m, 3H), 7.56 (m, 2H), 7.45 (dd, *J* = 7.1, 8.3 Hz, 1H), 7.30 (m, 3H), 7.25 (m, 1H), 7.18 (m, 1H), 6.78 (s, 1H), 6.55 (d, *J* = 8.7 Hz, 2H), 6.36 (m, 3H), 4.63 (s, 2H), 4.10 (s, 2H), 3.74 (s, 3H), 3.44 (m, 2H), 2.73 (m, 2H), 2.30 (m, 2H); MS (AP/Cl): 502.2 (M+H)+; minor isomer, characteristic 1H NMR signals: δ 4.66 (s), 4.12 (s), 2.60 (m).

Example 64. 2-naphthalen-1-yl-N-[5-(*cis*-3-phenyl-cyclobutyl)-1H-pyrazol-3-yl]-acetamide

A solution of N-[2-(4-methoxy-benzyl)-5-(3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide (Preparation 7.2, 38 mg, 0.076 mmol) in trifluoroacetic acid (5 mL) at room temperature was treated with anisole (165 uL, 1.5 mmol). The solution was heated at 70 °C for 5 h. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (40:1 chloroform–methanol) to afford 27 mg (89% yield) of the title compound as a 94:6 mixture of *cis* – *trans* isomers. The product was dissolved in ethyl acetate and treated with hydrogen chloride in diethyl ether to afford the HCl salt.

1H NMR (400 MHz, CD3OD): δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.50 (m, 4H), 7.28 (m, 4H), 7.17 (m, 1H), 6.26 (s, 1H), 4.27 (s, 2H), 3.59 (m, 2H), 2.82 (m, 2H), 2.30 (m, 2H); MS (AP/Cl): 382.3 (M+H)+.

The title compounds of the following Examples 65-71 were synthesized as in Example 64, including synthesis of Preparations 7.1 and 7.2, using an analogous starting ketone:

Example 65. N-{5-[*cis*-3-(2-Methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide

1H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.80 (dd, *J* = 1.7, 4.1 Hz, 1H), 7.93 (m, 2H), 7.54 (d, *J* = 1.7 Hz, 1H), 7.47 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.27 (q, *J* = 4.1 Hz, 1H), 7.15 (m, 2.79 (m, 2H), 2.29 (m, 2H); MS (AP/CI): 392.2 (M+H)+.

The following additional Examples of compounds of the invention were synthesized as described herein:

N-{5-[*cis*-3-(4-Hydroxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(3-Hydroxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

2-Naphthalen-1-yl-N-[5-(*cis*-3-pyridin-3-yl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-[5-(*cis*-3-Naphthalen-2-yl-cyclobutyl)-2H-pyrazol-3-yl]-2-pyridin-3-yl-acetamide;

N-(5-Indan-2-yl-1H-pyrazol-3-yl)-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-Pyridin-2-yl-cyclobutyl)-2H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

N-[5-(*cis*-3-Pyridin-2-yl-cyclobutyl)-2H-pyrazol-3-yl]-2-quinolin-6-yl-acetamide;

2-(4-Methoxy-phenyl)-N-[5-(*cis*-3-pyridin-4-yl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[3-(*cis*-2-Dimethylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[3-(2-Dimethylamino-ethoxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Hydroxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[2-(2-Dimethylamino-ethoxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-[5-(*cis*-3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(2-Fluoro-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[4-(Azetidin-3-yloxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[2-(Azetidin-3-yloxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[*cis*-3-(2-methylsulfanyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(2-Amino-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(4-Cyano-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Cyano-phenyl)-3-hydroxy-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Hydroxy-ethyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[3-(3-methylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(3-Cyclopropylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[*cis*-3-(3-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(3-Diethylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide; and

N-{5-[*cis*-3-(3-Azetidin-1-ylmethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide.

or, when R^7 and R^8 are as in NR^7R^8, they may instead optionally be connected to form with the nitrogen of NR^7R^8 to which they are attached a heterocycloalkyl moiety of from three to seven ring members, said heterocycloalkyl moiety optionally comprising one or two further heteroatoms independently selected from N, O, and S;

each R^{10}, R^{11}, *and* R^{12} *is independently selected from* H, *straight chain or branched* (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, and (5-14 membered) heteroaryl, wherein R^{10}, R^{11}, and R^{12} are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(=O)R^{14}$, $-NR^{13}C(=O)OR^{14}$, $-NR^{13}C(=O)NR^{14}R^{15}$, $-NR^{13}S(=O)_2R^{14}$, $-NR^{13}S(=O)_2NR^{14}R^{15}$, $-OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13}$, $-OC(=O)NR^{13}R^{14}$, $-OC(=O)SR^{13}$, $-SR^{13}$, $-S(=O)R^{13}$, $-S(=O)_2R^{13}$, $-S(=O)_2NR^{13}R^{14}$, $-C(=O)R^{13}$, $-C(=O)OR^{13}$, $-C(=O)NR^{13}R^{14}$, and R^{13};

each R^{13}, R^{14}, and R^{15} is independently selected from H, straight chain or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, and (5-14 membered) heteroaryl, wherein R^{13}, R^{14}, and R^{15} are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}C(=O)NR^{17}R^{18}$, $-NR^{16}S(=O)_2R^{17}$, $-NR^{16}S(=O)_2NR^{17}R^{18}$ $-OR^{16}$, $-OC(=O)R^{16}$, $-OC(=O)OR^{16}$, $-OC(=O)NR^{16}R^{17}$, $-OC(=O)SR^{16}$, $-SR^{16}$, $-S(=O)R^{16}$, $-S(=O)_2R^{16}$, $-S(=O)_2NR^{16}R^{17}$, $-C(=O)R^{16}$, $-C(=O)OR^{16}$, $-C(=O)NR^{16}R^{17}$, and R^{16}

each R^{16}, R^{17}, and R^{18} is independently selected from H, straight chain or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, and (5-14 membered) heteroaryl;

n is 0, 1, 2, or 3;

wherein R^{10} and R^{11} in $-C(=O)(CR^{10}R^{11})_n-$ and $-(CR^{10}R^{11})_n-$ are for each iteration of n defined independently as recited above;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^3 is $-(CR^{10}R^{11})_n-$, -C(=O)NH- or $-C(=O)(CR^{10}R^{11})_n-$.

3. A compound according to claim 1, wherein R^1 is optionally substituted (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl.

{5-[3-*cis*-(4-methoxy-benzylamino)-cyclopentyl]-1H-pyrazol-3-yl}-(3-trifluoromethyl-phenyl)-amine;

4-(5-cyclobutyl-2H-pyrazol-3-ylamino)-benzonitrile;

(5-cyclobutyl-2H-pyrazol-3-yl)-(3-fluoro-phenyl)-amine;

(5-cyclobutyl-2H-pyrazol-3-yl)-(3,5-dichloro-phenyl)-amine;

(2-bromo-phenyl)-(5-cyclobutyl-2H-pyrazol-3-yl)-amine;

N-{*cis*-3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-acetamide;

pyridin-2-yl-{3-*trans*-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amine;

(5-cyclobutyl-1H-pyrazol-3-yl)-(4-methoxy-phenyl)-amine;

pyridine-2-carboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide;

3-trifluoromethyl-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-benzamide;

cyclobutanecarboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide;

2,2-dimethyl-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-propionamide;

4-fluoro-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-benzamide;

2,2,2-trifluoro-N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-acetamide;

cyclopropanecarboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide;

N-{3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-propionamide;

cyclohexanecarboxylic acid {3-[5-(3-trifluoromethyl-phenylamino)-2H-pyrazol-3-yl]-cyclopentyl}-amide;

N-[5-(3-acetylamino-cyclopentyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide;

cyclopropanecarboxylic acid {3-[5-(2-naphthalen-1-yl-acetylamino)-1H-pyrazol-3-yl]-cyclopentyl}-amide;

2-naphthalen-1-yl-N-{5-[3-(2,2,2-trifluoro-acetylamino)-cyclopentyl]-2H-pyrazol-3-yl}-acetamide;

N-{3-[5-(2-naphthalen-1-yl-acetylamino)-1H-pyrazol-3-yl]-cyclopentyl}-benzamide;

N-(5-hydroxymethyl-1H-pyrazol-3-yl)-2-naphthalen-1-yl-acetamide;

2-naphthalen-1-yl-N-[5-(thiazol-2-ylaminomethyl)-1H-pyrazol-3-yl]-acetamide;

N-[5-((1S)-hydroxy-ethyl)-2H-pyrazol-3-yl]-2-naphthalen-1-yl-acetamide;

4-dimethylamino-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide;

3,5-dimethoxy-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide;

2-naphthalen-1-yl-N-[5-(*cis*-3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(3-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[*cis*-3-(4-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

2-naphthalen-1-yl-N-[5-(*cis*-3-*p*-tolyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(4-chloro-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

2-(4-methoxy-phenyl)-N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-phenyl-acetamide;

N-{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-pyridin-3-yl-acetamide;

N-{5-[*cis*-3-(4-methoxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

2-quinolin-6-yl-N-[5-(*cis*-3-*p*-tolyl-cyclobutyl)-1H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(4-fluoro-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

N-{5-[*cis*-3-(4-chloro-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-quinolin-6-yl-acetamide;

2-quinolin-6-yl-N-[5-(*cis*-3-*m*-tolyl-cyclobutyl)-1H-pyrazol-3-yl]-acetamide;

4-dimethylamino-N-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-benzamide;

2-naphthalen-1-yl-N-{5-[*cis*-3-(pyridin-2-yloxy)-cyclobutyl]-1H-pyrazol-3-yl}-acetamide;

6-methyl-pyridine-2-carboxylic acid {*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide;

2-phenyl-cyclopropanecarboxylic acid methyl-{*cis*-3-[5-(2-naphthalen-1-yl-acetylamino)-2H-pyrazol-3-yl]-cyclobutyl}-amide;

N-{5-[*cis*-3-(3-methyl-pyrazin-2-yloxy)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

{5-[*cis*-3-(2-methoxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-(6-methoxy-pyridin-2-yl)-amine;

N-{5-[3-(*cis*-2-Dimethylaminomethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[3-(2-Dimethylamino-ethoxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Hydroxy-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[2-(2-Dimethylamino-ethoxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-[5-(*cis*-3-phenyl-cyclobutyl)-2H-pyrazol-3-yl]-acetamide;

N-{5-[*cis*-3-(2-Fluoro-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[4-(Azetidin-3-yloxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

N-(5-{*cis*-3-[2-(Azetidin-3-yloxy)-phenyl]-cyclobutyl}-2H-pyrazol-3-yl)-2-(4-methoxy-phenyl)-acetamide;

2-(4-Methoxy-phenyl)-N-{5-[*cis*-3-(2-methylsulfanyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-acetamide;

N-{5-[*cis*-3-(2-Amino-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(4-Cyano-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Cyano-phenyl)-3-hydroxy-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Hydroxy-ethyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-naphthalen-1-yl-acetamide;

N-{5-[*cis*-3-(3-Cyano-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Cyano-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(3-Amino-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

4-(*cis*-3-{5-[2-(4-Methoxy-phenyl)-acetylamino]-1H-pyrazol-3-yl}-cyclobutyl)-benzoic acid methyl ester;

N-{5-[*cis*-3-(4-Hydroxymethyl-phenyl)-cyclobutyl]-2H-pyrazol-3-yl}-2-(4-methoxy-phenyl)-acetamide;

N-{5-[*cis*-3-(2-Hydroxy-phenyl)-cyclobutyl]-1H-pyrazol-3-yl}-2-phenyl-acetamide;

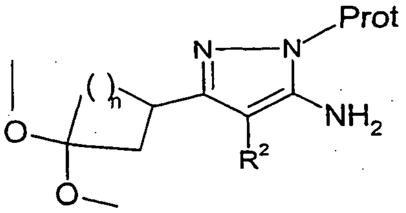
10. A pharmaceutical composition for treating a disease or condition comprising abnormal cell growth or a neurodegenerative disease or condition in a mammal comprising a compound of claim 1 in an amount effective in treating said disease or condition, and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition for treating a disease or condition in a mammal the treatment of which can be effected or facilitated by altering dopamine mediated neurotransmission comprising a compound of claim 1 in an amount effective in treating said disease or condition or in an amount effective to inhibit cdk5 activity, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for treating in a mammal a disease or condition selected from male fertility and sperm motility; diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and obesity; myogenesis and frailty, for example age-related decline in physical performance; acute sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency, comprising a compound of claim 1 in an amount effective in treating said disease or condition, and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a compound according to claim 1 and a second member selected from the group consisting of an SSRI, an NK-1 receptor antagonist, a $5HT_{1D}$ antagonist, ziprasidone, olanzapine, risperidone, L-745870, sonepiprazole, RP 62203, NGD 941, balaperidone, flesinoxan, gepirone, an acetylcholinesterase inhibitor, TPA, NIF, a potassium channel modulator such as BMS-204352, and an NMDA receptor antagonist, wherein the cdk5 inhibitor and the second member are together in an effective amount, and a pharmaceutically acceptable carrier.

14. A compound of the formula



I ;

wherein Prot is a protecting group;

R^2 is H, F, $-CH_3$, -CN, or $-C(=O)OR^7$;

and n is an integer selected from 1, 2, 3, and 4.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 62506 A (BURROWS JEREMY NICHOLAS ;BUTLIN ROGER JOHN (GB); NOWAK THORSTEN (G) 9 December 1999 (1999-12-09) claim 1; examples 239,318 ---	1,5, 10-13
X	DUMAS J ET AL: "1-Phenyl-5-pyrazolyl ureas: potent and selective p38 kinase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 18, September 2000 (2000-09), pages 2051-2054, XP004208309 ISSN: 0960-894X compound 28 ---	1,5,6, 10-13
X	TRAXLER P ET AL: "USE OF A PHARMACOPHORE MODEL FOR THE DESIGN OF EGF-R TYROSINE KINASE INHIBITORS: 4-(PHENYLAMINO)PYRAZOLO3,4-DPYRIMIDINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, no. 22, 1997, pages 3601-3616, XP001009913 ISSN: 0022-2623 page 3605 ---	1,6-8
X	WO 99 32106 A (BAYER AG) 1 July 1999 (1999-07-01) page 58 -page 65; claims; table 3 ---	1,5, 10-13
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRINKMEYER, RAYMOND S. ET AL: "Dimerization of pyrazolyl-5-hydroxypyrrolidinones to tetrazocines" retrieved from STN Database accession no. 112:216898 XP002183737 compound with RN=127056-78-4 & J. HETEROCYCL. CHEM. (1989), 26(6), 1713-17 , ---	1,3,4
P,X	WO 01 12189 A (BRASCA MARIA GRABRIELLA ;TRAQUANDI GABRIELLA (IT); ORSINI PAOLO (I) 22 February 2001 (2001-02-22) claim 1 ---	1-13
P,X	WO 01 12188 A (TRAQUANDI GABRIELLA ;ORSINI PAOLO (IT); PEVARELLO PAOLO (IT); VARA) 22 February 2001 (2001-02-22) claim 15 --- -/--	1-13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,5-8,10-13 (all partially)

Present claims 1, 2, 5-8,10-13 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds according to claim 3.

Furthermore, the search can be considered as complete for all claimed compounds with respect to publications disclosing the kinase activity of said compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.